PSYCHOLOGICAL ASPECTS OF CANNABIS USE AND CANNABIS USE DISORDER

EDITED BY: Daniel Feingold, Eva Hoch, Aviv M. Weinstein and Wayne Denis Hall

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PSYCHOLOGICAL ASPECTS OF CANNABIS USE AND CANNABIS USE DISORDER

Topic Editors:
Daniel Feingold, Ariel University, Israel
Eva Hoch, LMU Munich University Hospital, Germany
Aviv M. Weinstein, Ariel University, Israel
Wayne Denis Hall, The University of Queensland, Australia

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EDITORIAL
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Editorial: Psychological Aspects of Cannabis Use and Cannabis Use Disorder

Daniel Feingold[1]*, *Eva Hoch*[2,3], *Aviv Weinstein*[1] and *Wayne Hall*[4]

[1] Department of Psychology, Ariel University, Ariel, Israel, [2] Clinic and Policlinic of Psychiatry and Psychotherapy, Clinic of Ludwig-Maximilian-University, Munich, Germany, [3] Division of Clinical Psychology and Psychological Treatment, Department of Psychology, Ludwig-Maximilian-University, Munich, Germany, [4] National Centre for Youth Substance Use Research, The University of Queensland, St Lucia, QLD, Australia

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Editorial on the Research Topic

Psychological Aspects of Cannabis Use and Cannabis Use Disorder

An increasing global prevalence of cannabis use has produced increased treatment seeking for Cannabis Use Disorder (CUD) and an increased research effort to identify factors associated with initiation of cannabis use, transitions to regular cannabis use and the onset of CUD (1, 2). The majority of empirical studies focus on biological and psychiatric aspects of cannabis use and CUD, including the role of genetic and neurological factors as well as comorbid mental disorders in studying the etiology and phenomenology of cannabis use and CUD (3, 4). In recent years, emerging evidence points to the contribution of psychological, cognitive, and motivational factors to cannabis use and CUD (5).

In this Research Topic, we assembled a collection of research focusing on psychological aspects of cannabis use and CUD that brought together researchers from various psychological schools who employed diverse methodological practices (e.g., experimental research, narrative studies, theoretical writing). This collection of papers reviews the evidence which has been accumulated in that field, presents up-to-date findings, describes gaps in our knowledge and identifies future directions in research, practice, and policy.

Sorkhou et al. systematically reviewed 124 cross-sectional and longitudinal studies from 1990 to 2020 on adverse behavioral outcomes in cannabis users who did not have psychiatric and medical co-morbidities. The preponderance of the evidence suggested that the risks of adverse outcomes increased with the frequency of cannabis use, the THC (but not CBD) content of cannabis used, age of onset, and cumulative cannabis exposure. The strongest evidence was for psychosis and psychosocial functioning.

Preuss et al. reviewed systematic reviews, meta-analyses, and relevant papers published within the last decade on the contribution of cannabis use to car crashes. Meta-analyses and culpability studies consistently found a modest but significantly increased risk of crashes after acute cannabis use. These risks varied by study type, crash severity, and the method used to measure cannabis use. Some studies show a significant correlation between high THC blood concentrations and car crash risk but most studies did not find a relationship at lower THC concentrations. They did not find any scientifically supported cut-off concentration of THC in blood that could be used to define impaired driving. Further research was needed to assess dose-response effects of cannabis use on neuropsychological functioning related to driving skills and crash risk.

Brands et al. discuss key questions regarding the possible effect of cannabis legalization on impaired driving and road safety. According to the authors, emerging evidence indicate that driving

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Francesco Paolo Busardò, Marche Polytechnic University, Italy

***Correspondence:**
Daniel Feingold
danielfe@ariel.ac.il

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under the influence of cannabis may increase the risk for collision and contribute to deaths and injuries resulting from collisions and young adults are the most likely to drive under the influence of cannabis. The acute effects of cannabis on driving-related behaviors include an increase in weaving, reduction in speed, and prolonged reaction time. The authors call for further research, exploring topics such as the specific effects of cannabis use on collisions types and injury severity, sex differences in the effects of cannabis and the impairing effects of medical cannabis use on driving.

López-Pelayo et al. used Classification and Regression Trees (CART) analyses to identify the independent and integrated effects of cannabis use patterns on self-reported cannabis-related harms in a large sample of cannabis users. The results indicated that early onset of regular cannabis use and current frequent cannabis use increased the probability of risky alcohol use. In addition, early onset of regular cannabis use in combination with prolonged regular use was associated with increased odds of a motor vehicle accident. Current daily or near daily cannabis use was independently associated with screening positive for a cannabis use disorder.

Leung et al. reviewed studies conducted between 1973 and 2020 that examined whether cannabis users who used higher THC content cannabis products can and do titrate the doses of THC that they receive. They included (1) experimental laboratory studies of dose titration; (2) observational studies of users of more potent products; and (3) surveys on whether cannabis users titrate when using more potent products. Some experiments found inverse associations between the THC content of cannabis and the amount smoked and smoking topography but in others higher THC doses were consumed and more marked psychological and physiological effects observed. In some surveys, cannabis users reported that they use less of more potent cannabis products, but in other surveys, persons who used more potent cannabis reported more adverse effects of use, suggesting that they received higher THC doses. They concluded that we need better experimental and epidemiological research to inform regulatory policies to minimize harms from the use of high THC cannabis products.

De la Peña-Arteaga et al. systematically reviewed studies of the association between exposure to childhood physical and sexual abuse and adolescent cannabis use. They included 13 studies, eight of which had a low risk of bias. Eleven papers found a modest relationship between childhood sexual abuse and adolescent cannabis use [OR 1.29 (95% CI 1.08–1.49)] and 7 found a modest relationship between childhood physical abuse and adolescent cannabis use [OR 1.39 (95% CI 1.12–1.66]. The strength of the evidence varied with the method of exposure ascertainment. There was some evidence of differences in association by gender, age of cannabis initiation, and the severity of the abuse. Further work is needed on the role played by adolescent cannabis use in the causal pathway between childhood abuse and adult mental health problems.

Claus et al. assess the relationship between the severity of cannabis withdrawal syndrome (CWS) and urine cannabinoid concentrations in 78 adult cannabis-dependent subjects. They used a commercial enzyme immunoassay of 11-nor-9-carboxy-Delta-9-tetrahydrocannabinol (THC-COOH) to assess subjects 13 times during a 24-day inpatient detoxification treatment. Absolute urinary THC-COOH levels were significantly correlated with Marijuana Withdrawal Checklist scores ($r = 0.248$; $p < 0.001$) but after adjustment for serial creatinine ratios the correlation was significant only in the sample with higher MWC scores (>11 points) at admission ($n = 21$; $r = 0.247$; $p = 0.002$). These relationships persisted when they examined day-to-day change in THC-COOH-levels. MWC scores were significantly correlated with the Clinical Global Impression-Severity (CGI-S; $r = 0.812$; $p < 0.001$). Females showed a significantly slower decline in urine THC-COOH levels and more prolonged CWS course and substantial illness severity (per CGI-S) in nearly 30% of cases.

Gullo et al. explored the utility of a bioSocial Cognitive Theory in treating cannabis use disorders. Social Cognitive Theory (SCT) emphasizes the importance of targeting two psychological mechanisms: drug outcome expectancies and low drug refusal self-efficacy. They outlined a new bioSocial Cognitive Theory (bSCT) that integrated findings from the literature and presented preliminary evidence that treatment based on this approach improved outcomes in persons with cannabis use disorders.

Serebro et al. undertook a narrative exploration of cannabis use disorder among young Israeli combat veterans who used cannabis to cope with PTSD symptoms. They used narrative analysis to interpret retrospective in-depth interviews with 12 combat veterans who were released from mandatory military duty during the past 5 years and qualified for a diagnosis of a CUD. Participants came from a larger quantitative study of veterans who screened positive for a diagnosis of CUD on the Cannabis Use Disorder Identification Test- Revised (CUDIT-R) questionnaire. Five main themes were identified: (a) traumatic events, (b) attitudes toward cannabis use, (c) combatant identity, (d) the role of authority/father figures, and (e) moral crisis. A meta-theme was "from enchantment to disillusion" which represented a gradual shift from a hopeful, highly motivated stance into a state of mental rupture and moral injury, which they unsuccessfully treated by their excessive use of cannabis. This study highlighted the role that use of cannabis for "self-medication" of trauma symptoms contributed to a sense of betrayal.

Lorenzetti et al. assessed the residual effects of chronic cannabis use and abstinence on verbal and visuospatial learning. Regular cannabis users differ from non-using controls in learning performance but it is unclear (i) if these differences are specific to distinct domains of learning (verbal, visuospatial), (ii) if these differences increase with cannabis exposure and (iii) if they dissipate after sustained abstinence. They examined different domains of learning (verbal, visuospatial) in current and abstaining cannabis users, and the role of chronicity of use in 127 psychiatrically healthy participants (65 female) with mean aged of 34 years, of whom 69 were current regular cannabis users (mean 15 years use), 12 were former cannabis users who had been abstinent for ∼2.5 years (after 16 years use), and 46 were non-cannabis using controls. Current cannabis users performed worse than non-users on verbal learning (Long Delay Cued Recall) and

visuospatial learning (Retroactive Interference and LD Rotated Recall). Prolonged abstinence was associated with altered verbal learning but intact visuospatial learning.

López-Pelayo et al. argue that a standardized measure of cannabis dose is a priority for research that will inform policy-making, the design of clinical and harm-reduction interventions and improve consumer safety. They propose that a Standard Joint Unit (SJU) be developed for cannabis. A back-casting foresight method was used to achieve consensus on developing an SJU with 32 professionals from 13 countries and 10 disciplines. Several characteristics of the SJU were defined: (1) core values: easy-to use, universal, focused on THC, accurate, and accessible; (2) key challenges: sudden changes in patterns of use, heterogeneity of cannabis products and administration routes, variations over time in THC concentrations and laws that regulate recreational and medical cannabis use; and (3) facilitators: previous experience with standardized measurements, funding opportunities, multi-stakeholder support, high prevalence of cannabis users, and widespread changes in legislation. Participants identified three steps for the implementation of a SJU by 2030: (1) building a task-force to develop a consensus-based SJU; (2) expanding national-level data; and (3) linking SJU consumption to "risky use" based on evidence of harms.

Sofis et al. conducted an exploratory study on the effect of cannabis use frequency and training on episodic memory, specifically on the recall of specific and rewarding events. Active cannabis users were randomly assigned to receive a brief intervention aimed at enhancing specificity of event retrieval (Episodic Specifity Induction: ESI) or a control group. They were categorized according to their intensity of past-month cannabis use. Results indicated higher levels of vividness and excitement ratings in the low vs. high intensity and ESI vs. control groups. No significant interaction was observed, suggesting that frequent cannabis use may be associated with the retrieval of less specific and rewarding events, which may be compensated by ESI.

Allick et al. conducted a systematic review and meta-analysis of voxel-based morphometry studies of cortical gray matter volume (GMV) in adolescent (12–21 years old) cannabis users. They used PRISMA guidelines and effect-size seed-based d mapping meta-analyses to compare age- and sex-related differences between cannabis using and typically developing youth. Six whole-brain voxel-based morphology studies were analyzed that included 357 cannabis users and 404 non-users. Meta-analysis did not identify any region showing significant GMV differences but age and sex differences were identified in meta-regressions: younger cannabis users showed increased superior temporal gyrus (STG) volume and older users showed decreased STG compared to age-matched controls. The authors conclude that GMV abnormalities in teen cannabis users are subtle and may be partially attributed to age and sex differences.

In conclusion, cannabis can have both therapeutic effects and adverse consequences [see (3, 6) for reviews]. This collection of papers has evaluated the behavioral and cognitive outcomes of cannabis including driving safety and verbal and visuospatial learning. Other studies looked at the association between exposure to childhood physical and sexual abuse and adolescent cannabis use and the use of cannabis for treating PTSD symptoms. The pharmacology of dose titration and the association between measures of THC and withdrawal has also been explored. Finally, studies have evaluated outcome of treatment and the residual effects of chronic cannabis use and abstinence on verbal and visuospatial learning in adult users and cortical gray matter volume in adolescent cannabis users. We hope that this collection will be a positive contribution to this exciting field of research.

AUTHOR CONTRIBUTIONS

DF, WH, and AW wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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ORIGINAL RESEARCH
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Is the Urine Cannabinoid Level Measured via a Commercial Point-of-Care Semiquantitative Immunoassay a Cannabis Withdrawal Syndrome Severity Predictor?

Benedikt Bernd Claus[1], *Michael Specka*[2], *Heath McAnally*[3], *Norbert Scherbaum*[2], *Fabrizio Schifano*[4] *and Udo Bonnet*[1,2]*

[1] Department of Psychiatry, Psychotherapy and Psychosomatic Medicine, Evangelisches Krankenhaus Castrop-Rauxel, Academic Teaching Hospital of the University of Duisburg-Essen, Castrop-Rauxel, Germany, [2] Department of Psychiatry and Psychotherapy, Faculty of Medicine, LVR-Hospital Essen, University of Duisburg-Essen, Essen, Germany, [3] Department of Anesthesiology and Pain Medicine, University of Washington School of Medicine, Seattle, WA, United States, [4] Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hatfield, United Kingdom

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Daniel Feingold,
Ariel University, Israel

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Columbia University Irving Medical Center, United States
David Gorelick,
University of Maryland School of Medicine, United States

***Correspondence:**
Udo Bonnet
udo.bonnet@uni-due.de

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Background: For cannabis-dependent subjects, the relationship between cannabis withdrawal syndrome (CWS) severity and the urine cannabinoid concentrations are unclear; we investigated this using a commercial point-of-care (POC) enzyme immunoassay detecting 11-nor-9-carboxy-Delta-9-tetrahydrocannabinol (THC-COOH).

Methods: Observational study of 78 adult chronic cannabis-dependent subjects assessed over a 24-day inpatient detoxification treatment, with 13 serial measurement days. Repeated Measures Correlation and Multilevel Linear Models were employed.

Results: Absolute urinary THC-COOH levels significantly correlated with Marijuana Withdrawal Checklist (MWC) scores across the entire study duration ($r = 0.248$; $p < 0.001$). Correlation between serial creatinine-adjusted THC-COOH ratios and serial MWC scores emerged as significant only in the sample with higher MWC scores (>11 points) at admission ($n = 21$; $r = 0.247$; $p = 0.002$). The aforementioned significant relationships have persisted when replacing the absolute THC-COOH-levels with the (relative) day-to-day change in urinary THC-COOH levels. MWC scores were significantly correlated with the Clinical Global Impression-Severity (CGI-S; $r = 0.812$; $p < 0.001$). Females showed a significantly slower decline in urine THC-COOH levels and prolonged CWS course characterized by substantial illness severity (per CGI-S), occurring in nearly 30% of cases.

Conclusion: Urine cannabinoid levels (THC-COOH) determined by POC assay significantly predicted CWS severity (moderate correlation), guiding detoxification treatment duration. In patients with MWC > 11

points upon admission, creatinine-adjusted THC-COOH ratios also significantly predicted CWS severity—again with moderate effect size. Females showed prolonged urinary THC-COOH elimination and cannabis withdrawal.

Keywords: urinary 11-nor-9-carboxy-delta9-tetrahydrocannabinol, gender effect, cannabis withdrawal syndrome subtypes, protracted withdrawal syndrome, inpatient detoxification treatment

INTRODUCTION

The abrupt cessation of frequent cannabis intake is followed by a cannabis withdrawal syndrome (CWS), primarily presenting with emotional and behavioral symptoms (1–3). In US adults frequently using cannabis, the prevalence of CWS was 12.1% (4). Moreover, CWS is a key component of the cannabis dependence syndrome (CDS) as defined in ICD-10, with nearly 90% of these individuals displaying clinically relevant CWS (5). The cannabinoid receptor type 1 (CB_1) is thought to play a major role in CWS occurrence (3, 6, 7). Discontinuation of synthetic cannabinoids (which are generally full CB_1 agonists) (6) leads to a similar withdrawal syndrome (3); conversely, CB_1 agonists alleviate CWS symptoms (3, 7).

Over the past 20 years, clinical characteristics of CWS have been described in many out- and inpatient as well as epidemiologic studies (1, 3). Operationalized CWS criteria were first provided in DSM-5 (8) and await revision and expansion in ICD-11 (3), with the magnitude of CWS severity generally associated with the extent and duration of cannabis use before quitting (1, 3, 7). The severity of CWS in heavy users is comparable with the burden of a moderate major depressive episode, a moderate alcohol withdrawal syndrome (9) or tobacco withdrawal (10), at times requiring in- (9) or outpatient (10) treatment.

The main psychotropic agent of natural cannabis is delta-9-tetrahydrocannabinol (THC) which is a CB_1 partial agonist (3, 6). Main metabolites of THC include the psychotropic, water-soluble 11-hydroxy-delta-9-tetrahydrocannabinol (THC-OH), and the nonpsychotropic and lipophilic 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH) (11). THC-COOH undergoes conjugation with glucuronic acid prior to excretion in the urine (12, 13) where it serves as a biomarker of cannabis use in commercial point-of-care drug screening tests (14, 15). However, urine THC-COOH levels alone cannot be used to determine either the timeframe or the amount of the last cannabis use (11, 16, 17). In Germany, where inpatient detoxification of cannabis users undergoing significant levels of CWS is supported by statutory health insurance (3), the termination of the inpatient detoxification treatment phase is often empirically determined by the observation of consistent urine THC-COOH levels below a cutoff point of 50 ng/ml (the sensitivity limit of most immunoassays) (14) which corresponds to the US federally mandated immunoassay cutoff concentration (18). However, it is unclear whether levels of this biomarker—as measured by point-of-care testing (POCT)—are really associated with CWS severity in clinical practice, which influences treatment decisions regarding discharge and subsequent outpatient rehabilitation treatment for CDS (3). Greater-severity CWS is not only associated with increased likelihood of CDS but also with increased comorbidity and negative psychosocial outcomes (1–4). The answer to the question of whether an easily determined POCT biomarker predicts CWS severity thus assumes greater importance in the context of resource allocation.

Toward that end, we investigated the correlation between the clinical CWS course of cannabis-dependent persons seeking inpatient detoxification treatment and the trends of their urine cannabinoid levels as measured by the semiquantitative DRI® Cannabinoid Assay (15). This inpatient environment allowed for good control of major potential confounding factors such as cannabinoid relapse, concomitant hidden drug or alcohol use, and environmental psychosocial stress and comorbidities (9). We also examined the potential confounding issues of intentional dilution and adipose tissue cannabinoid redistribution by assaying for both creatinine- and BMI-normalized urine cannabinoid levels (11–13).

METHODS

Study Design, Participants, and Eligibility Criteria

This prospective observational study was conducted from 2008 to 2014 in an inpatient unit for detoxification from alcohol, prescription, and recreational drug abuse including cannabis at the Psychiatric University Hospital in Essen (LVR-Klinikum Essen), Germany. Adult detoxification-seeking patients who had a cannabinoid-positive urine screen upon admission were eligible. Only those patients who (a) were older than 18 years, (b) were diagnosed with cannabis dependence according to ICD-10 (19), (c) had used cannabis by inhalation daily or near-daily during the 6 months before admission, (d) reported use of cannabis within the 24 h prior to admission, (e) had used no other psychotropic substances (apart from tobacco) during the 4 weeks prior to admission, (f) presented with no active comorbid psychiatric or somatic disorder requiring treatment, (g) were familiar with the German language, and (h) gave their written informed consent were retained in the study. Inpatient treatment was scheduled for up to 24 days; however, patients could be discharged earlier based upon a shared patient/staff decision, when both parties agreed that the individual's psychiatric and somatic condition had improved to the point that primary or secondary care would be sufficient for continuation of treatment. In some cases, after inpatient stabilization, patients were referred to rehabilitation clinics for further treatment and support.

Exclusion Criteria

Patients with documented (e.g., through breath analysis or urinalysis) relapse to use of cannabis or other substances

including alcohol were excluded from the study. If there was reasonable suspicion of undisclosed Z-drugs (e.g., zolpidem, zaleplon, or zopiclone) or new psychoactive drugs (20), special urinalysis or serologic assays were performed and/or sent for detailed or confirmatory analysis to MVZ Synlab Leverkusen GmbH, Leverkusen, Germany, or the Division of Forensic Medicine at the University of Duisburg-Essen, Germany.

A ratio of 1.5 or greater between two serial creatinine-normalized urine THC-COOH values was interpreted as indication of relapse to marijuana use (21). In such cases, as previously described (9), blood THC-OH concentrations were assessed by gas chromatography-mass spectroscopy (GC-MS) for confirmation, and when an increase over admission baseline THC-OH was confirmed, the patient was excluded from the study on the basis of apparent cannabis relapse (9).

Dropout Criteria

Dropouts included (a) premature self-discontinuation of treatment, (b) withdrawal of study participation consent, or (c) development of a relevant comorbidity requiring intervention and stabilization.

Treatment Regimen, Including Medication-on-Demand

The multimodal inpatient treatment program consisted of a diverse regimen including regular medical assessments, individual and group psychotherapeutic sessions based upon motivational enhancement, cognitive-behavioral treatment elements and psychoeducation, physical and occupational therapies, and social counseling. In addition, the option for postdischarge transfer to a long-term rehabilitation program was offered to all patients. When patients showed distressing withdrawal symptoms such as anxiety, dysphoria, restlessness, or sleep disturbance, the nursing staff was allowed to administer escalating doses of gabapentin (22) (up to 600 mg q.i.d) or chlorprothixene (up to 50 mg q.i.d.) as medication-on-demand (PRN). For potential subanalysis purposes, an equipotency ratio assuming 50 mg chlorprothixene equivalent to 400 mg gabapentin was used.

Measurements

Upon admission to detoxification treatment, a structured interview was administered to all patients to determine sociodemographics, addiction-related information (e.g., age at first cannabis use, amount and duration of daily cannabis use, other comorbid substance abuse), psychiatric and other relevant medical and social information. Substance use during the previous 6 months was assessed using a timeline follow-back interview (23). Body mass index (BMI) was determined upon admission (day 1). During detoxification treatment the severity of CWS was measured by a modified version of the Marijuana Withdrawal Checklist (MWC) (9, 24) and the Clinical Global Impression scale-Severity of Illness (CGI-S) (25). In its original version, the MWC consists of 10 symptoms (craving for cannabis, irritability, nervousness/anxiety, restlessness/tension, depression, anger/aggression, sleeplessness, strange dreams, loss of appetite, headache) which are rated on a 4-point scale (0 = not at all, 1 = mild, 2 = moderate, 3 = heavy) (25). Consistent with prior investigation carried out by our group (3, 9) two more clinically relevant and validated (2, 7, 10) symptoms (sweating and nausea) were added to the original MWC. The MWC was administered as a face-to-face interview by UB or by other trained physicians.

The MWC, CGI-S, and urine drug testing (see below) were performed at admission, on the next day (day 2) and subsequently every other second day until the end of the inpatient treatment period. Potential relapses were assessed during medical reviews with the help of breathalyzer and random urine drug screens (see "Exclusion Criteria").

Urine Cannabinoid-Analysis and Related Ratios

In clinical practice, urinary immunoassays (IA) provide immediate confirmation and detection of reported and unreported drug use, respectively (11, 14). Commercially available cannabis IA show good specificity for cannabinoids with minimal false-positive cross-reactivity from other substances (11). For this investigation, we utilized a convenient semiquantitative POCT instrument, the DRI® Cannabinoid Assay ("DRI®" (15), analyzed by a Beckmann-Coulter AU 400 chemistry analyzer.

DRI® identifies the following cannabinoids: THC, THC-OH, THC-COOH, 11-OH-delta-8-THC-COOH, 8-beta-OH-delta-9-THC, 8-beta-11-OH-delta-9-THC, and cannabidiol. DRI® provides a cannabinoid measurement range between 0 and 200 ng/ml if the analyzer is calibrated using the 200 ng/ml THC-COOH calibrator (15). Using Dri® Drugs of Abuse Immunoassays for urine screening, a sensitivity and a specificity of 91 and 96%, respectively, were observed for the detection of cannabinoids (THC-COOH, Assay cut off 4 IA-units) (26). Using a 50-ng/ml THC-COOH cutoff calibration, DRI® has demonstrated 100% accuracy verified by GC-MS with a 15 ng/ml cutoff (15). We therefore used the 200-ng/ml calibrator recommended by the manufacturer and a 50-ng/ml cutoff. For simplicity, the urine cannabinoid levels as measured by DRI® were here reported as THC-COOH levels (see also below in the "Discussion—Limitations" section). To account for the role of body fat in storage and multicompartmental pharmacokinetic redistribution of the lipophilic THC molecule and metabolites (11, 12), serial THC-COOH concentrations were adjusted for BMI (B-N-THC-COOH) and reported as nanograms per milliliter THC-COOH per kilogram square meter. To adjust for dilution or concentration of urine specimens (11), we furthermore calculated creatinine-normalized THC-COOH concentrations (C-N-THC-COOH) by dividing all serial THC-COOH concentrations by the urine creatinine concentration (g/L) with results reported in nanograms THC-COOH per milligram of creatinine (16). Creatinine levels were determined by IA from the same urine sample assayed for cannabinoids, and any sample with a creatinine concentration <20 mg/dl was considered to be adulterated (11).

Statistics

For the intention-to-treat (ITT) analysis, we used descriptive statistics. Repeated Measures Correlation (rmcorr) for the

TABLE 1 | Sociodemographic and clinical variables of the ITT sample of cannabis-dependent subjects admitted for an inpatient detoxification treatment.

Study population	*N*	%	Median	Mean (SD)	Min.	Max.
Age (years old)	78	100	24	26.4 (7.0)	18	51
Females	18/78	23				
BMI (kg/m²)	73	93.6	22.4	22.5 (3.0)	16.5	29.5
Age (years) at first-ever cannabis use	73	93.6	17	18.0 (4.8)	9	33
Duration (years) of cannabis use prior to admission	73	93.6	8	9.4 (2.2)	0.25	36
Daily amount (g) of cannabis inhalation during the 6 weeks prior to admission	73	93.6	2	2.2 (1.5)	0.5	10
(Tobacco) cigarettes per day	72	92.3	20	18.6 (7.8)	0[a]	40
Patients requiring PRN medication	44	56.4				
Patients without educational qualifications	04	5.1				
Patients with primary school education	31	39.7				
Patients with secondary school education	18	23.1				
Patients with general university entrance certificate (Abitur)	05	6.4				
Patients having completed vocational training	26	33.3				
Unemployed patients	38	48.7				
Patients with a history of psychiatric comorbidity	33	42.3				
Patients with a history of somatic comorbidity	4	5.1				

[a] *Three patients reported nil use of nicotine.*

estimation of correlations between two measures being recorded at multiple time points (27) was used to analyze the relationship between urine THC-COOH levels (or B-N-THC-COOH or C-N-THC-COOH ratios) and MWC scores across the study. Furthermore, we investigated the relationship between day-to-day change in urinary THC-COOH (delta THC-COOH) and MWC-scores (see **Supplementary Material**). For the investigation of influences on the temporal course of these measurements, we used Multilevel Linear Models (MLM) (28). The following control variables (possible confounders) were included in the model: age, gender, age at index cannabis use, daily amount and duration of cannabis inhalation prior to admission, prior amounts of daily cigarettes, prior psychiatric comorbidity (yes or no), and in addition, the daily gabapentin dose (22). In the MLM framework, we observed multiple measurements (level 1) for multiple participants (level 2) (28).

We also performed subgroup analyses as well based on whether patients presented with low (2–11 points) or high (12–21 points) MWC scores at admission.

With ongoing attrition of patients no longer suffering from significant CWS and thus leaving treatment, we noted an inflection point at day 16 with significant increases in average CWS (as well as THC-COOH levels) seen among patients remaining in treatment at that point (**Figure 2**; **Supplementary Figure 2**). As such, we chose to stratify the sample into "early" vs. "late" discharge subgroups based on when their discharge occurred in relationship to that mark. Comparisons between early and late discharged patients were carried out using Welch's t tests and χ^2 tests as well as MLM regression analysis (see **Supplementary Material**).

For all tests, a significance criterion of $p < 0.05$ was used. We used IBM SPSS Statistics 21 and R (29) for our analyses, with the R package nlme (30) for MLMs. Correlation coefficients (Pearson's r) were defined as small ($r > 0.1$), medium ($r > 0.2$), and large ($r > 0.3$) (31).

RESULTS

Sample

During the 6-year study period, 2017 detoxification treatments were carried out on the ward, with 735 of these admissions characterized by cannabinoid positivity on initial urine screen and 97 of these meeting the inclusion criteria. Eight of these however were repeat admissions of the same individual (doublets) and 11 patients declined participation, yielding a study population of 78 patients (all white) being included in the ITT analysis. Sociodemographic and clinical variables are shown in **Table 1**. Mean (SD) BMI was not significantly different between females [22.4 (2.93)] and males [22.5 (2.99); $t_{(24.44)} = -0.136$, $p = 0.893$]. Psychiatric comorbidity histories included borderline personality disorder, major depression, panic disorder, insomnia, and ADHD. Somatic comorbidities included allergic bronchial asthma, gastro-esophageal reflux disease, ulcerative colitis, and arthropathies not otherwise specified. Of these, none worsened during the detoxification treatment to an extent requiring further treatment.

Treatment Durations and Attrition Rate

Nine (11.5%) participants dropped out of the study. All of these patients discontinued inpatient treatment prematurely, within days 4–13; remaining patients ($n = 69$, 88.5%) underwent planned discharge. The attrition rate (dropouts plus regularly discharged patients) is illustrated in **Figure 1**. The mean (SD) inpatient detoxification lasted 14.6 days (6.5), with a median of 14 days, and minimum of 6 and maximum of 24 days.

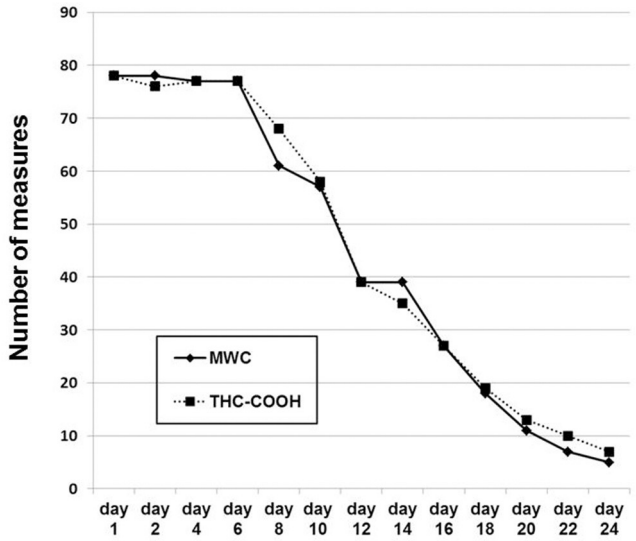

FIGURE 1 | The number of serial investigations across the study. The number of patients remaining in the study is equivalent to the maximal number of any measure at any given day. Day 1, day of admission. At every study day, MWC was always linked to a CGI-S measurement.

PRN Medication

See **Supplementary Material**.

Postdischarge Treatment

Most treatment completers ($n = 37$, 47.4% of all patients) were referred to an outpatient program at the same clinic (32) while 21 patients (26.9%) were referred to a specialized long-term rehabilitation facility.

Course of Measured Variables

Figure 1 shows the number of the serial MWC ratings and urinary THC-COOH measurements across the study. Their decreasing numbers over time reflect the nine dropouts and regular discharge of patients as outlined above in **Figure 1**. **Figure 2** shows the values of the measurements across the study. The striking transient deterioration between days 16 and 22 correlated with the removal of a "dilution effect" exerted by improved patients leaving treatment prior to day 16.

Relationship Between CWS and Urine THC-COOH Across the Study

Using *rmcorr*, which analyzes the relationship between MWC and the respective metabolite ratios at every point of measurement, positive correlation was identified between MWC and THC-COOH ($r = 0.248$ [0.152, 0.339], $df = 388$, $p < 0.001$). A significant positive correlation was also found between MWC and B-N-THC-COOH ($r = 0.249$ [0.154, 0.341], $df = 388$, $p < 0.001$). The association between MWC and C-N-THC-COOH was not significant ($r = 0.096$ [−0.004, 0.195], $df = 382$, $p = 0.059$).

To account for possible confounding variables (listed above in the "Statistics" section), we used MLM. The random intercept and random slopes models were in all cases superior to the intercept-only and random intercept-only models (see "Statistics"). The chosen random intercept and slopes models' calculations provided the following results: a significant association was confirmed between MWC scores and THC-COOH ratios ($b = 0.026$ [0.014, 0.037], $p < 0.001$). The models also demonstrated a significant positive association between MWC scores and B-N-THC-COOH ($b = 0.572$ [0.338, 0.805], $p < 0.001$). Finally, the relationship between MWC scores and C-N-THC-COOH ratios also emerged as significant ($b = 0.005$ [0.0002, 0.009], $p = 0.040$), with the daily gabapentin dose being the decisive factor, $b = 0.001$ [0.0005, 0.002].

Influence of Admission (Baseline) CWS Severity

For those patients ($n = 21$) who presented with high CWS severity (12–21 MWC points) upon admission, C-N-THC-COOH values significantly correlated with the MWC scores across the whole study ($r = 0.247$ [95% CI, 0.094 to 0.39]; $p = 0.002$). This association remained significant after incorporating the control variables into the model ($b = 0.011$ [95% CI, 0.003 to 0.019]; $p = 0.006$). Conversely, for those 46 subjects who presented at admission with low CWS severity (2–11 MWC points), no significant correlation was identified with C-N-THC-COOH ratios across the whole study ($r = -0.043$ [95% CI, −0.173 to 0.088]; $p = 0.519$; $b = 0.0004$ [95% CI, −0.005 to 0.005]; $p = 0.891$).

Predictors of CWS and Urine THC-COOH Values (as well as the Ratios)

To further clarify the above-described associations, we analyzed time course and a range of remaining control variables (see "Methods—Statistics") as possible predictive factors influencing MWC scores, urine THC-COOH levels, C-N-THC-COOH, and B-N-THC-COOH ratios. Again, the random intercept and random slopes models were in all cases superior to the other models of MLM; the respective results of these models are presented below.

MWC Scores

MLM revealed the factor "time" to be significant ($p = 0.009$) with a negative regression coefficient (b) of −1.078 [95% CI, −1.873 to −0.284]. In other words, the MWC score decreased 1.08 points on average from measurement to measurement when all control variables were held constant. The other significant association noted was that between MWC scores and Gabapentin dose ($b = 0.001$ [95% CI, 0.0006 to 0.002]; $p = 0.003$), i.e., the higher the daily gabapentin dose, the higher the MWC scores. The remaining variables did not significantly predict the MWC score.

Urine THC-COOH Levels

Time was identified as a significant factor ($p = 0.003$) in predicting urine THC-COOH levels with a negative regression weight (b) of −13.562 [95% CI, −22.492 to −4.632]. In other words, with remaining variables being held constant, THC-COOH ratios decreased from measurement to measurement by over 13 points on average. Age at first-ever cannabis use also

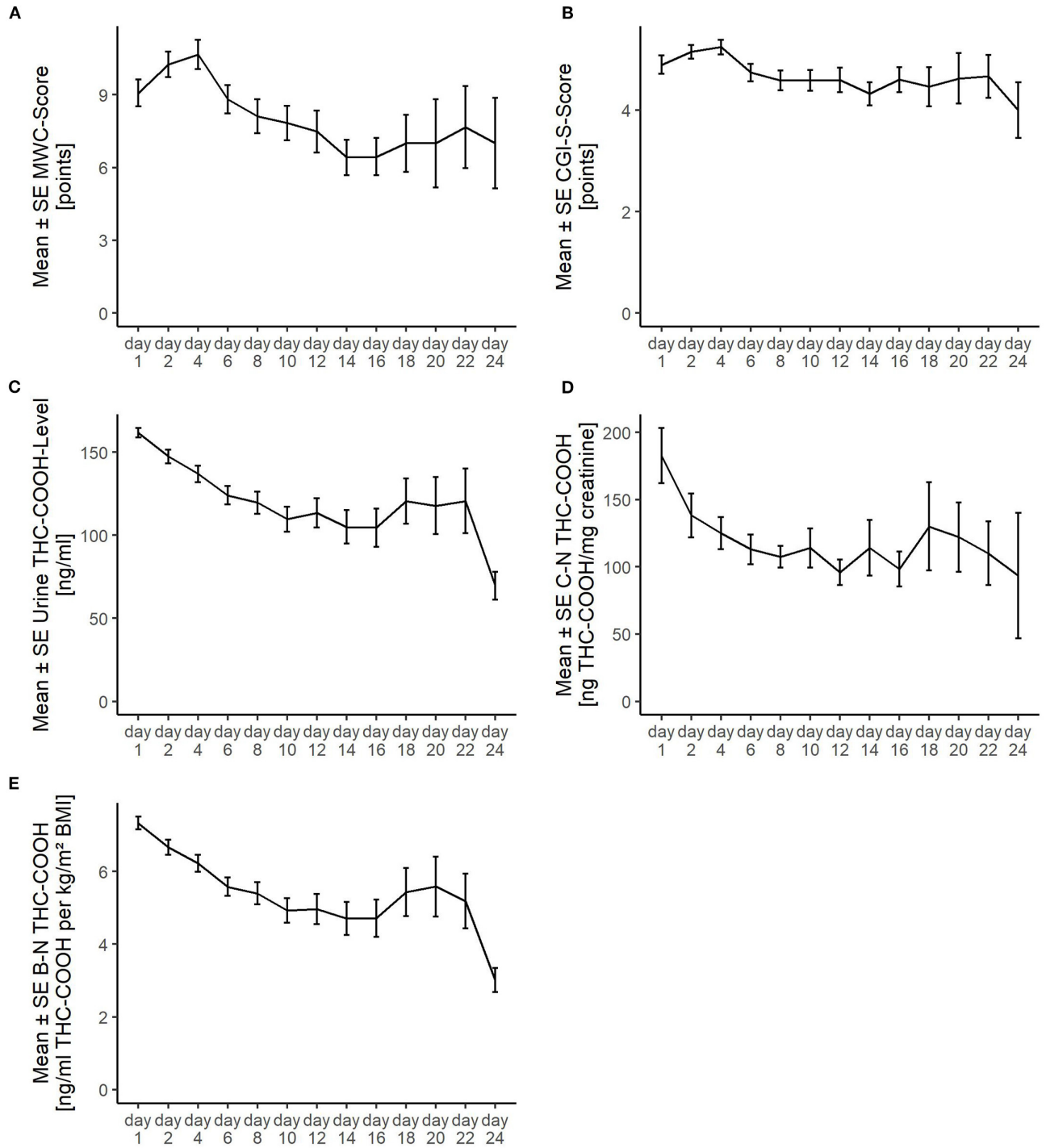

FIGURE 2 | Course of the detoxification treatment as measured **(A)** via the Marijuana Withdrawal Checklist (MWC); **(B)** Clinical Global Impression-Severity (CGI-S); **(C)** levels of urinary 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (Urine THC-COOH); **(D)** creatinine-normalized THC-COOH (C-N-THC-COOH); and **(E)** BMI-normalized THC-COOH (B-N-THC-COOH). SE, standard error. The striking transient deterioration between days 16 and 22 correlated with the removal of a "dilution effect" exerted by improved patients leaving treatment prior to day 16.

emerged as a significant predictor ($b = -3.391$ [95% CI, −6.491 to −0.291]; $p = 0.035$) with higher THC-COOH ratios for those with an earlier onset of cannabis use. The interaction between time and gender was significant as well ($b = -4.549$ [95% CI, −8.721 to −0.377]; $p = 0.035$), indicating a faster decline of THC-COOH levels in male patients.

C-N-THC-COOH Ratios

For all urine samples, creatinine was >20 mg/dl. Neither "time" nor the other control variables influenced the C-N-THC-COOH ratios significantly.

B-N-THC-COOH Ratios

The factor "time" was significant ($p < 0.001$) with a negative regression weight ($b = -0.731$ [95% CI, −1.154 to −0.308]). In other words, with the other variables held constant, B-N-THC-COOH ratios decreased from measurement to measurement by 0.73 points on average. The interaction between time and gender was also significant ($b = -0.219$ [95% CI, −0.417 to −0.020]; $p = 0.033$), indicating a faster decline of B-N-THC-COOH levels in males. The remaining control variables did not influence the B-N-THC-COOH ratios significantly.

Using the Day-to-Day Change in Urinary THC-COOH Levels (Delta THC-COOH-Levels) Instead of the Absolute THC-COOH Levels

All aforementioned significant relationships and influences identified by using the absolute urinary THC-COOH levels as outcome variable were confirmed by substituting these by using the relative delta THC-COOH levels (**Supplementary Figure 1**). The other results were also not altered as the relationships and influences remained insignificant (see **Supplementary Material**).

Relationship Between MWC and CGI-S Scores

Using rmcorr, a significant correlation between MWC and CGI-S scores was identified ($r = 0.812$ [95% CI, 0.776 to 0.843]; $p < 0.001$). Using MLM to adjust for the influence of control variables, the relationship between MWC and CGI-S scores remained significant, with $b = 3.310$ [95% CI, 2.972 to 3.652], and $p < 0.001$.

Early- vs. Late-Discharged Patients

See **Supplementary Material**.

DISCUSSION

Serial Positive Correlation of Urine THC-COOH and CWS Across the Study and Factors Influencing Their Slopes

Individuals seeking inpatient detoxification for their CDS—without other significant comorbidities/coexisting substance use disorders—are relatively rare in our experience, as reflected in the prolonged recruitment and study period of 6 years. To the best of our knowledge, this study is the first to demonstrate the significant association between urine THC-COOH levels and CWS severity, which proved to be a robust finding via regression analyses, rmcorr and MLM. The strength of the association however was moderate at best ($r = 0.248$) and disappeared when evaluating creatinine-adjusted cannabinoid levels ($r = 0.096$, $p = 0.059$). A significant positive correlation however between these variables (C-N-THC-COOH and MWC) was restored if PRN medication use was left in the model. As we have also found that the PRN medication significantly predicted the CWS severity, it was likely that a significant correlation between MWC scores and C-N-THC-COOH ratios may be observed in patients with high CWS levels only. Indeed, this was the case in patients with MWC scores >11 points at admission, again with moderate effect size ($r = 0.247$).

The Controversial Role of Creatinine-Adjusted Drug Screens in Routine Practice

To reduce the influence of urine dilution upon measured drug and metabolite values, creatinine adjustment or normalization is recommended as the scientific standard, including the assaying of urine THC levels (11). However, such adjustment is not generally carried out in routine practice, which typically relies only on threshold or cutoff measurement/detection (33). The reliability of the urine creatinine level as a "dilution marker" is also limited by the effects of protein concentration in the diet, muscle mass, physical activity and even emotional stress, and urine creatinine level may accordingly vary greatly throughout the day (34, 35). As such, it must be understood that urine creatinine level at any given point in time comprises a single "snapshot."

One could speculate that PRN medication altered urine concentration by an effect on GFR or solute reabsorption. Neither mechanism however has been shown at therapeutic doses of gabapentin or chlorprothixene to the best of our knowledge nor has an additive osmolar effect (more solute, i.e., gabapentin or chlorprothixene in the urine).

Gender Effect

Urine THC-COOH levels decreased significantly faster in males, while females remained longer in the study (i.e., >16 days), suggesting a protracted withdrawal in females. This is consistent with previous studies showing worsened CWS levels in females vs. males (7, 9).

BMI and Other Factors Putatively Influencing Both CWS- and Urinary THC-COOH Slopes

The rapid decline in urinary THC-COOH levels in males appeared to be independent from BMI normalization, and this may argue against a prolonged redistribution phase of THC from adipose tissue deposits (13, 14) as the key factor for delayed urine elimination of THC-COOH (12, 13). Similarly, no correlation between BMI and plasma THC levels in chronic cannabis smokers during 7 abstinent days was identified (36).

Female and male BMI levels were not significantly different in this study population, which may suggest that the suggested gender-specific differences in both THC elimination and protracted CWS may not necessarily be the consequence of body composition differences. Conversely, one could argue that BMI may not be the best marker to identify the individual fat proportion and distribution. In order to better characterize the potential role of adiposity on cannabinoid metabolism and elimination, alternate methods such as skin caliper testing, Dual

Energy X-ray Absorptiometry (DEXA), or Magnetic Resonance Imaging (MRI) might be considered (37).

Neither age, amount, or duration of prior cannabis intake nor history of comorbidities were shown to influence MWC, THC-COOH, or their interaction in this study. Furthermore, although age at initial cannabis use predicted urine THC-COOH levels, it did not predict either CWS severity or the positive association between THC-COOH and MWC.

PRN Medication Effectiveness

See **Supplementary Material**.

Replacing the Absolute THC-COOH Levels With the Day-to-Day Change in THC-COOH Levels

Using each day's absolute THC-COOH level (**Figure 2C**) is not the same as day-to-day change in level (**Supplementary Figure 1**). It seems plausible that it is the degree of THC-COOH decline itself, not the absolute level, that indirectly drives withdrawal [provided that the THC-COOH decline is closely related with the THC decline which pharmacologically drives withdrawal (3, 11, 13)]. However, we found no relevant differences regarding our results when replacing the absolute THC-COOH levels with the (relative) day-to-day change in urinary THC-COOH levels as an outcome variable (see **Supplementary Material**). In this context, it should be emphasized that all patients reported that their last cannabis use had taken place within the last 24 h before admission (according to our inclusion criteria). Thus, this time span seems to be appropriate for our accuracy purposes.

Protracted CWS and THC-COOH Elimination

Most of the study population (e.g., the "early" group; $n = 58$ including dropouts) had been discharged normally before day 16 due to sufficient clinical improvement levels. Conversely, the findings of the "late" group ($n = 20$), presenting with both considerable CWS intensity and urine THC-COOH levels, may indicate the existence of a distinct subset of THC users—around 30% in our sample—characterized by a protracted withdrawal course (38–40). The symptom patterns and trajectories of these two groups are consistent with those of the previously postulated CWS subtypes A and B (3), respectively. It would be worth investigating whether genetic variations of cannabis-metabolizing enzymes account for these subtypes' differences (13, 41).

In our late-discharged group, the average THC-COOH values did not drop below the cutoff value of 50 ng/ml even after 24 abstinent days. While this is in line with previous findings (42, 43), it also supports the existence of a special population among chronic cannabis users with a delayed THC terminal-phase elimination from the body (16, 43–46). While prolonged CWS courses have previously been described and ascribed to psychiatric comorbidities (39, 40), our late group showed no such association with psychiatric comorbidity nor with age nor cannabis history data. What we did find was a disproportionate female preponderance within the late group, with increased urine THC-COOH levels, but not with MWC scores. These observations are consistent with previous observations of females experiencing a more complicated CWS than males (3, 7). An alternative explanation would be that the patients in the late group had consumed cannabis during the study period; the likelihood of such occurrence was however here minimized by the measures utilized to detect possible hidden drug and alcohol use.

Serial Positive Correlations Between MWC and CGI-S

The present study confirmed our previous findings that the MWC score is a valuable predictor of the disease burden experienced by patients with CDS abstaining from use, as measured via the CGI-S (9). Notably, in patients with a protracted CWS ($n = 20$, 27.4%), the average CGI-S score did not drop over time below the 4-point mark, indicating: "…overt symptoms causing noticeable but functional impairment or distress…" (25). This demonstrates a persistent illness burden in a subgroup of heavy/long-term cannabis users despite detoxification, who may require more intensive postdetox rehabilitation (3). It could be argued that durable executive and social deficits (47, 48) were the main factors behind the functional impairment of this (primarily female) group demonstrating slower elimination of cannabinoids and protracted CWS, and these phenomena might be amplified by potential gender differences in the regulation of the brain endocannabinoid system (7). As a side note, this constellation of pharmacokinetic and pharmacodynamic differences might also explain the observation that females seem to progress more rapidly from first regular cannabis use to cannabis dependence than males (7).

Cognitive functions of this group may also have been affected by residual plasma THC [as with more recently abstinent chronic cannabis users (3, 44)], but this hypothesis is not consistent with recent findings (49).

Strengths of the Study

This study provides insight into the course of CWS among treatment-seeking adult CDS patients during detoxification, and is the first to investigate the feasibility of utilizing a simple urine-based POCT to prognosticate about the likely severity of CWS. The sample was relatively large for this type of study, allowing for adequate study power to investigate not only routine variables such as gender, but also less frequently considered variables including BMI, urine creatinine concentration, etc.

Limitations of the Study

Immunoassays are well known to yield false-positive results (15), and for optimal specificity, more accurate GC-MS assays should be employed (11, 13). The point of this study however was to investigate the potential of a convenient, point-of-care, semiquantitative IA for use under routine inpatient conditions. Inherent in the methodology therefore is the risk that the cannabinoids identified measured by the DRI® test may not have exclusively comprised THC-COOH. Nonetheless, this main THC metabolite increases in the urine within a few hours after

cannabis use, with specificity/accuracy increasing over time, paralleling the number of abstinent days (11, 12, 49). Although one could also hypothesize patients' intentional use of adulterants to produce false-negative urine screens (50), all patients sought treatment of their own accord and presented with a high degree of motivation, lessening the likelihood of such deception.

A ratio of 1.5 (21) for comparison of later-to-earlier C-N-THC-COOH levels was used here as evidence of hidden/undisclosed cannabis relapse. Although this value has been criticized because of its potential low sensitivity, the utilization of a lower ratio of 0.5 (13, 44) did not alter our results (data not shown here).

Consistent with other studies focusing on gender effect on CWS severity (7), we did not control for female participants' menstrual period phase, which may have influenced CWS severity levels.

Roughly half of the patients had been discharged by day 12, which lowers the statistical power over the second half of the study. However, the utilization of both rmcorr and MLM regression analyses should reduce inaccuracies and biases associated with that attrition (27, 28); see also **Supplementary Material**—Methods.

Our results are rather specific for detoxification units in our country which, for cannabis is usually performed in psychiatric hospitals with similar personnel and material structures. However, for the general population of cannabis users, our results may not be representative.

We did not perform a direct analysis of the association between urine cannabinoid levels (by POCT) and the severity of CDS or cannabis use disorder (CUD) which should comprise a future project. It would also be interesting to expand this investigation to the outpatient treatment arena, where environmental stress and CWS might be more intense and prolonged, and might yield a greater association between urine cannabinoid levels and CWS than the moderate one demonstrated in this inpatient study. In this context, a more detailed investigation of the change of the co-use of daily nicotine alongside further studies to these issues would be particularly informative as concurrent tobacco use and possible tobacco withdrawal may modulate the severity of CWS, CDS, and cannabis use (1, 3, 11). Ignoring concurrent tobacco use is a major limitation of the present study. The same applies as for the fact that we did not determine the exact time of the last cannabis use of the participants, which, however was within the last 24 h before admission (see inclusion criteria in the "Methods" section and the section further above where the results after replacing the absolute THC-COOH-levels with the day-to-day change in THC-COOH levels are discussed). Self-reported time of last cannabis use has some limitations. However, using this variable with more direct pharmacological relationship to the outcome variable (CWS), even though it has some measurement limitations, might be a sophisticated alternative to using an objective variable with assumably weaker pharmacological relationship to the CWS as we did with defining the date of admission as temporal baseline. As we used self-reports to inform about remote and recent drug history, reporting or recall bias might have also influenced our results. To mitigate this bias for the CWS rating, we performed MWC face to face as well as the CGI-S.

CONCLUSIONS

Throughout this 24-day study, the urine THC-COOH levels significantly predicted the severity of CWS, as measured by the MWC. After creatinine adjustment, serial THC-COOH values significantly correlated with serial MWC scores only in those subjects with high MWC scores (>11 points) at admission. The correlation levels were generally moderate ($r \sim 0.25$). Female gender correlated significantly with both a delayed decrease in urine cannabinoid levels and with prolonged CWS. According to the CGI-S, these CWS levels were characterized by significant illness severity, which is consistent with a previously postulated "nonpeaking" CWS-subtype B (3). Conversely, those patients with a nonprotracted CWS showed the typical "peaking" character of the CWS-subtype A (3), which is more commonly seen and reported. The levels of MWC and CGI-S were here strongly correlated ($r = 0.81$), suggesting that the CDS disease burden is comparable with that of other medical conditions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics commitee of the Medical Faculty of the University of Duisburg-Essen. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

UB: conception, design, data collection, and drafting the article. BC and MS: analysis of the data. All authors interpretation of data and revising the manuscript critically for important intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.598150/full#supplementary-material

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SYSTEMATIC REVIEW
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The Behavioral Sequelae of Cannabis Use in Healthy People: A Systematic Review

Maryam Sorkhou[1,2], *Rachel H. Bedder*[3] *and Tony P. George*[1,2,4]*

[1] *Addictions Division, Centre for Addiction and Mental Health (CAMH), University of Toronto, Toronto, ON, Canada,* [2] *Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada,* [3] *Department of Psychology, Ryerson University, Toronto, ON, Canada,* [4] *Department of Psychiatry, University of Toronto, Toronto, ON, Canada*

Background: Cannabis is known to have a broad range of effects on behavior, including experiencing a "high" and tranquility/relaxation. However, there are several adverse behavioral sequalae that can arise from cannabis use, depending on frequency of use, potency (e.g., THC content), age of onset, and cumulative exposure. This systematic review examined evidence for cannabis-related adverse behavioral sequalae in otherwise healthy human subjects.

Methods: Following PRISMA guidelines, we conducted a systematic review of cross-sectional and longitudinal studies from 1990 to 2020 that identified cannabis-related adverse behavioral outcomes in subjects without psychiatric and medical co-morbidities from PubMed and PsychInfo searches. Key search terms included "cannabis" OR "tetrahydrocannabinol" OR "cannabidiol" OR "marijuana" AND "anxiety" OR "depression" OR "psychosis" OR "schizophrenia" "OR "IQ" OR "memory" OR "attention" OR "impulsivity" OR "cognition" OR "education" OR "occupation".

Results: Our search detected a total of 2,870 studies, from which we extracted 124 relevant studies from the literature on cannabis effects in the non-clinical population. Effects of cannabis on several behavioral sequelae including cognition, motivation, impulsivity, mood, anxiety, psychosis intelligence, and psychosocial functioning were identified. The preponderance of the evidence suggests that frequency of cannabis use, THC (but not CBD) content, age of onset, and cumulative cannabis exposure can all contribute to these adverse outcomes in individuals without a pre-existing medical condition or psychiatric disorder. The strongest evidence for the negative effects of cannabis are for psychosis and psychosocial functioning.

Conclusions: Although more research is needed to determine risk factors for development of adverse behavioral sequelae of cannabis use, these findings underline the importance of understanding vulnerability to the adverse effects of cannabis, which has implications for prevention and treatment of problematic cannabis use.

Keywords: cannabis, healthy subjects, cognition, mood, anxiety, psychosis, motivation, intelligence

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Daniel Feingold,
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***Correspondence:**
Tony P. George
tony.george@camh.ca

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INTRODUCTION

Following nicotine and alcohol, cannabis is the most commonly used psychoactive substance in the world, with a global prevalence of 5.1% in 2016 (1, 2). Cannabis is an illegal substance in most countries but is increasingly becoming a legal drug in various states in the USA, in Portugal and Uruguay, and, as of 2018, nationwide in Canada (3). The trend toward legalization of recreational cannabis use corresponds with heightened acceptance, reduced perception of risk, and an increase in cannabis use among adolescents and adults (4–6).

Cannabis contains over 100 distinct cannabinoids, several of which have demonstrated psychoactive properties (7). Two of the most widely researched cannabinoids are delta-9-tetrahydrocannabinol (THC), and cannabidiol (CBD), which directly modulate the endocannabinoid system in humans. The endocannabinoid system is comprised of at least two cannabinoid receptor types, CB1 and CB2, which are involved in various brain functions, including pain, motivation, memory, mood, and reward processing (8, 9).

THC is the principal psychoactive constituent of the cannabis plant and produces a wide range of transient and dose-dependent effects by acting as an agonist at CB1 receptors (10). In animal models, THC administration reduces anxiety at low doses but increases anxiety at higher doses (11). It also produces transient psychotomimetic effects, including perceptual distortions, paranoia, and euphoria (12). There is evidence that acute administration of THC interferes with numerous behavioral and cognitive processes, including emotional processing, episodic memory, attention, working memory, and reward processing [e.g., (13–15)].

In contrast to THC, CBD has a low affinity for CB1 and CB2 receptors, and its molecular mechanism of action remains poorly understood (7). CBD is thought to inhibit the hydrolysis and reuptake of endocannabinoids and modulate cannabinoid receptors (16, 17) CBD produces markedly different psychological effects in comparison to THC and does not adversely impact cognitive or motor performance during intoxication (18, 19). CBD is devoid of any psychomimetic effects, and both human and animal evidence suggests that CBD has anxiolytic properties (20, 21). Co-administration of CBD and THC may alter the pharmacological effect of THC, such that CBD enhances some of THC's desirable effects while attenuating some of its adverse effects (20, 22–24). For example, a recent systematic review investigating CBD's psychoactive properties, suggested that CBD may offset the psychosis-like effects of THC (25).

Recently, there have been concerns surrounding the increased levels of THC found in present day cannabis, combined with reduced levels of CBD (26). This high-potency cannabis is gaining popularity with recreational users despite a growing body of literature indicating that potent cannabis preparations are associated with adverse health outcomes, including increased risk of psychosis, hypomania, impulsivity, and cannabis use disorder (27–29). Furthermore, with substantial legalization, decreased perceptions of risk associated with cannabis may arise, which may further increase current cannabis use prevalence. For example, nationally representative data from adults across the United States indicated that the perceived risk of recreational cannabis use decreased from 51.3% in 2002 to 40.3% in 2012 (30), even though the THC potency of cannabis has increased from 8.9% in 2008 to 17.1% in 2017 (31). These changes in perception of risk emphasize the need for continued research on the behavioral effects of cannabis use, since there is significant variance concerning the potential harms and benefits of cannabis use.

This systematic review examines experimental, cohort, and cross-sectional studies to determine the effects of cannabis use on behavioral, cognitive, mental health and psychosocial adverse outcomes in non-clinical populations. We sought to address the following aims: (1) to determine the effects of cannabis use on the prevalence and severity of adverse outcomes in people without medical or psychiatric disorders and (2) to determine risk factors associated with the development of adverse outcomes in cannabis users.

METHODS

Search Strategy

Using PubMed and PsycINFO, original, peer-reviewed research articles were searched for based on the PRISMA guidelines by two of the authors (MS and RB) (See **Figure 1**) (32). Articles available online in the English language between 1990 through the end of October, 2020 were considered. Search terms (found in the title or abstract) utilized to obtain relevant articles were: "cannabis" OR "tetrahydrocannabinol" OR "cannabidiol" OR "marijuana" AND "anxiety" OR "depression" OR "psychosis" OR "schizophrenia" "OR "IQ" OR "memory" OR "attention" OR "impulsivity" OR "cognition" OR "motivation" OR "education" OR "occupation." Titles and abstracts were screened for relevance by two of the authors (MS and RB), and articles passing this stage were downloaded and assessed for eligibility via full-text review by MS. All uncertainties were assessed and resolved by the senior author (TPG).

The inclusion criteria were: (1) Original studies with experimental, cross-sectional, or cohort designs; (2) studies in which the sample at baseline demonstrated no current medical condition or history of a psychiatric disorder with the exception of cannabis use disorder; (3) studies utilizing validated or objective measures to evaluate cannabis use (e.g., urine toxicology, scores from The Cannabis Use Disorders Identification Test [CUDIT], etc.) (4) studies utilizing validated or objective measures to evaluate the primary outcome (e.g., hospital records, scores from the Beck Depression Inventory, graduation GPA, etc.).

The exclusion criteria were: (1) reviews, meta-analyses, and case studies. Additionally, we employed the Newcastle Ottawa Scale (NOS) to evaluate the quality of eligible cross-sectional and cohort studies in the review (33). The NOS allows a maximum score of nine and evaluates studies on three broad domains; (1) the selection of the study groups; (2) the comparability of the groups; and (3) the verification of the outcome of interest. Studies receiving a score of 5 or lower on the NOS indicated a high risk of bias, and consequently were excluded from the review (See

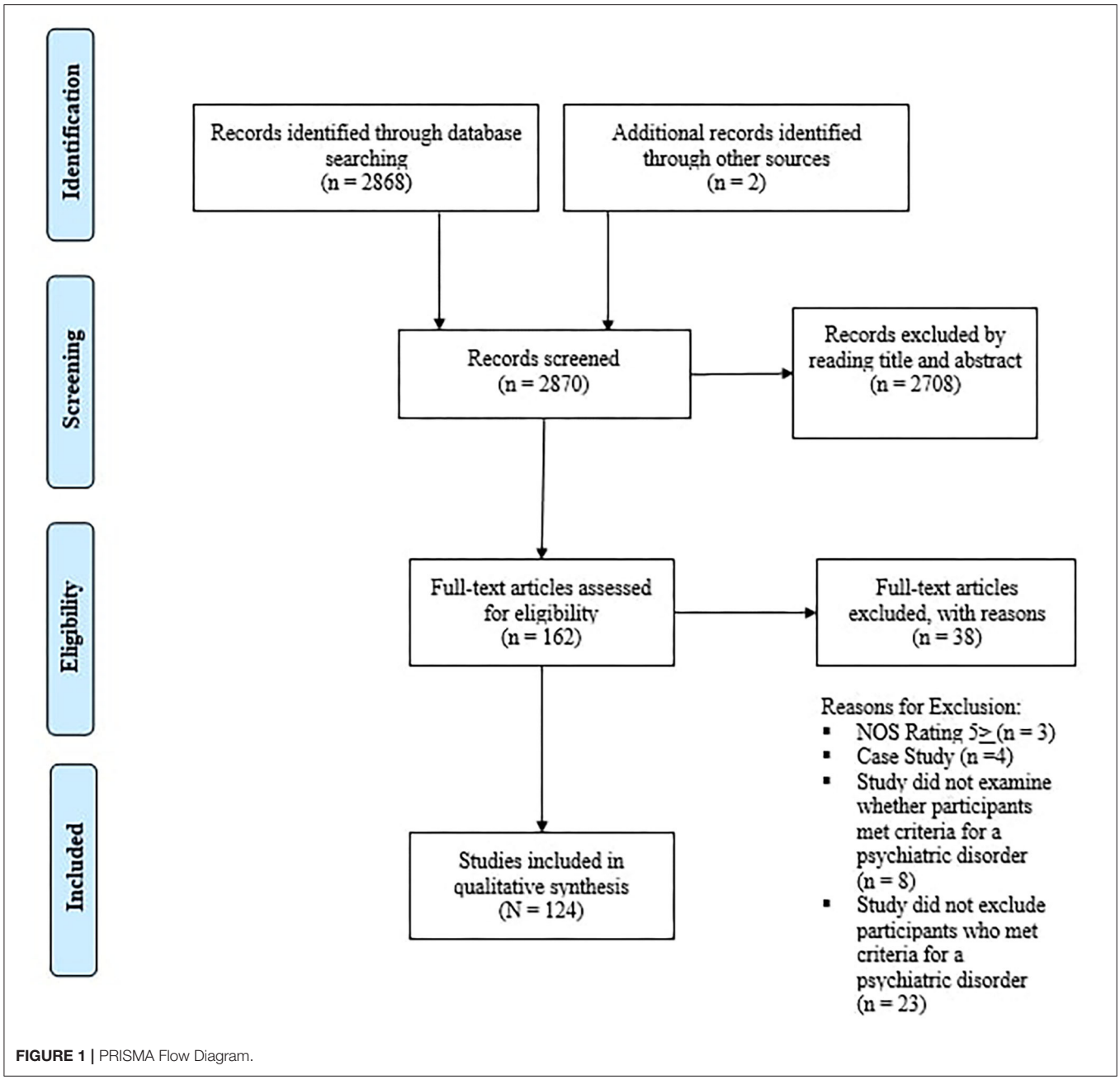

FIGURE 1 | PRISMA Flow Diagram.

Supplementary Tables 2,**3** for the quality ratings of the included and excluded studies, respectively).

Evidence Ratings

We recorded the following variables from each study: author, publication year, study design, sample size, study population, follow-up time, outcome measures, level of cannabis use, matched variables, and relevant findings (see **Supplementary Table 1** for further information). To determine whether there is a dose-dependent relationship between cannabis and the primary outcomes, we adapted a classification system utilized by Batalla et al. (34) which evaluated levels of cannabis use. We classified both cross-sectional and experimental designs. Cannabis dependent persons are those who meet the criteria for cannabis use disorder on the DSM-5 or DSM-IV at the time of the study. Chronic cannabis users are persons who do not meet the DSM-5 or DSM-IV criteria for cannabis use disorder but use cannabis 3+ times a week for at least 1 year. Recreational cannabis users are persons who use cannabis between one and four times a month, and controls were persons use had used cannabis <10 times in their lifetime.

To determine whether the accumulated evidence implicates a neutral or negative effect of cannabis for each domain, we calculated the proportion of studies evincing a negative effect of

cannabis use against the total number of studies (See **Table 2** for a summary of the level of evidence ratings) as follows:

1 = 0–19% corresponds with strong evidence of no effects of cannabis use
2 = 20–39% corresponds with moderate evidence of no effects of cannabis use
3 = 40–59% corresponds with mixed evidence of neutral or negative effects of cannabis use
4 = 60–79% corresponds with moderate evidence of negative effects of cannabis use
5 = 80–100% corresponds with strong evidence of negative effects of cannabis use.

RESULTS

We identified 2,870 hits of which 159 were considered potentially relevant, based on title and abstract inspection (See **Figure 1** for methods overview). Detailed examination of the potentially relevant publications reduced the sample to 127 studies that were within the inclusion criteria set for this systematic review. However, after examining the quality of eligible studies via the NOS, three studies were excluded from the review. Overall, 124 studies were included in the review with publication dates ranging from 1995 to 2020. Studies were conducted in a broad range of countries, and comprised of 48 cohort designs, 26 placebo-controlled, counter-balanced, experimental designs, and 50 cross-sectional designs (see **Table 1**).

Cognition

Memory

Four longitudinal studies evaluating the impact of cannabis use and memory were included (35, 42, 47, 63). Becker et al. (35) investigated differences among multiple cognitive domains within daily, adolescent, cannabis users and non-users at baseline and 2 years later. At follow-up, cannabis users demonstrated significant impairments in working memory and verbal learning relative to non-users. Moreover, an earlier age of cannabis use onset corresponded with more severe impairments at follow-up. Similarly, following a birth cohort of 1,037 individuals, Meier et al. (47) assessed neurocognitive functioning in participants at ages 13 and 38, while assessing cannabis use at ages 18, 21, 26, 32, and 38. Persistent cannabis use beginning in adolescence corresponded to impairments in working memory and verbal learning, in addition to other neurocognitive domains. However, a recent 14 year longitudinal study following adolescents annually, found no relationship between cannabis or alcohol use and performance in tasks evaluating verbal memory (63). Moreover, in a study comparing the effects of extended (28 day) of cannabis abstinence and reinstatement of cannabis use in people with schizophrenia vs. healthy controls with cannabis use disorder, there were no significant effects of 28 days of cannabis abstinence or reinstatement on verbal learning, verbal memory (% retention on HVLT-R task), and visuospatial memory in healthy controls, as compared to significant (>40%) improvements in verbal learning and memory with abstinence and impairment with cannabis use reinstatement in schizophrenia patients (62).

Twelve cross-sectional designs found no significant impairments in memory among cannabis users (24, 56–60, 64–69). Three of these studies investigated visuospatial working memory and independently employed fMRI to investigate potential differences in brain activity (67–69). Interestingly, although the three studies failed to suggest a behavioral deficit in cannabis users, the researchers all found unusual brain activity in cannabis users while performing the visuospatial memory task. Additionally, four other cross-sectional designs concluded no significant impairments among cannabis users in working memory (57–60). An fMRI study assessing working memory among a small sample of abstinent but frequent cannabis-using adolescents obtained no behavioral impairments on the task (60). However, during the task, cannabis users demonstrated increased brain activity in regions implicated in working memory, suggesting a reliance on neural compensatory strategies. These neurofunctional results were obtained in a similar study which found neural differences between cannabis users and non-users on a Sternberg-type working memory task, but no behavioral differences (57). In another study comparing adult, chronic cannabis users and controls on tests evaluating visuospatial memory, verbal memory, and executive functioning over a 28 day period, cannabis users demonstrated significant deficits in verbal memory during the first week of abstinence, but by Day 28, any significant differences between groups diminished (66). Moreover, no relationship between cannabis use frequency and performance at Day 28 emerged, presenting evidence for re-instatement of cognitive abilities with abstinence.

In contrast, 11 cross-sectional designs concluded that cannabis use is associated with memory impairments (24, 36, 39, 40, 43–46, 48, 49, 56). Morgan et al. (24) investigated whether the type of cannabinoid that users consumed led to differing impairments in memory. Splitting cannabis users into high THC/high CBD and high THC/low CBD groups, individuals who smoked high THC/high CBD cannabis did not demonstrate any deficits in immediate or delayed recall on an episodic memory task (24). However, high THC/low CBD users performed significantly worse on the task assessing episodic memory, leading to the authors' proposition that CBD may attenuate the harmful effects of THC on cognition. Additionally, three studies comparing 2–4 week cannabis abstinent users and non-users on measures of verbal learning and memory indicated that despite abstinence, users performed significantly worse than non-users (40, 44, 49). However, one of these studies found that among a 21 day cannabis abstinence intervention, slight improvements in verbal memory were obtained in cannabis users between Weeks 2 and 3, indicating partial recovery of neurocognitive functioning (40).

Similarly, the majority of experimental studies in which healthy volunteers received varying doses of THC suggest a negative impact of cannabis use on verbal learning, episodic memory, and working memory (13, 37, 41, 50, 51, 53). A recent study examined acute and delayed effects of THC intoxication on susceptibility to false memory among occasional cannabis users (50). Intoxicated participants generated significantly more

TABLE 1 | Review of evidence for acute and chronic effects of cannabis use on behavioral outcomes.

Behavioral Outcome Measured	Negative Effects	References	Positive or Neutral Effects	References	Conclusions
Verbal, Episodic, and Working Memory (*N* = 37)	There is evidence that acute and chronic cannabis use beginning in adolescence is associated with impairments in working memory, episodic memory, and verbal learning	(13, 24, 35–56)	Other evidence suggests that cannabis use is not associated with impairments in episodic memory, verbal working, or verbal learning	(14, 35, 56–66)	Overall, there is a moderate level of evidence implicating a negative relationship between cannabis use and verbal, working, or episodic memory. A total of 24/37 (64.9%) of included studies assessing these behavioral sequelae observed a negative effect of cannabis use
Visuospatial Memory (*N* = 6)	Only one experimental study found that THC administration corresponds with impairment in visuospatial memory	(41)	Most evidence suggests that cannabis use is not associated with impairments in visuospatial memory or visuospatial working memory	(40, 66–70)	There is little evidence implicating a relationship between cannabis use and impairments in visuospatial memory. Only 1/6 (16.7%) of included studies assessing this behavioral sequela observed a negative effect of cannabis use
Attention (*N* = 20)	There is evidence that chronic cannabis use is associated with impairments in divided attention and sustained attention	(36, 40, 53, 64, 70–77)	Other evidence that chronic cannabis use is not associated with impairments in selective attention	(35, 44, 48, 57, 62, 66, 78, 79)	Overall, there is a moderate level of evidence implicating a negative relationship between cannabis use and attention. 12/20 (60%) of included studies assessing this behavioral sequela observed a negative effect of cannabis use
Processing Speed (*N* = 6)	There is evidence that cannabis use and acute THC intoxication is associated with impairments in information processing	(36, 64, 72)	There is other evidence that chronic cannabis use does not lead to impairments in information processing	(56, 63, 65)	Overall, there is a mixed level of evidence implicating a negative relationship between cannabis use and processing speed. 3/6 (50%) of included studies assessing this behavioral sequela observed a negative effect of cannabis use
Executive Function (*N* = 20)	There is evidence from multiple study designs that cannabis use is associated with impairments in executive functioning, decision-making, and planning	(35, 47, 49, 74, 77, 80–86)	There is other evidence that chronic cannabis use does not impair executive functioning	(44, 48, 62, 65, 66, 87–89)	There is a moderate level of evidence implicating a negative relationship between cannabis use and executive function. 12/20 (60%) of included studies assessing this behavioral sequela observed a negative effect of cannabis use
Impulsivity/Inhibitory Control (*N* = 17)	There is evidence that acute THC intoxication and cannabis use beginning in adolescence is associated with greater impulsivity or impairments in inhibitory control	(41, 44, 48, 63, 71, 74, 90–93)	However, some studies assessing acute THC intoxication or chronic cannabis use in adults is not associated with greater impulsivity or impairments in inhibitory control	(35, 38, 56, 70, 94–96)	There is a mixed level of evidence implicating a negative relationship between cannabis use and inhibitory control. 10/17 (58.8%) of included studies assessing this behavioral sequela observed a negative effect of cannabis use
Intelligence (IQ) (*N* = 7)	There is some evidence that cannabis use beginning in adolescence is correlated with a minor decrease (1–2 points) in IQ in adulthood	(47, 55, 86)	Other evidence suggest that chronic cannabis use does not impact global IQ in adulthood after adjusting for potential confounds	(42, 97–99)	There is a mixed level of evidence implicating a negative relationship between cannabis use and intelligence. 3/7 (42.7%) of included studies assessing this behavioral sequela observed a negative effect of cannabis use
Motivation (*N* = 6)	There is evidence supporting the view that chronic cannabis users demonstrate amotivation and reduced reward processing than non-users	(100–103)	Two case-control studies found that cannabis use is not associated with impairments in motivation	(104, 105)	There is a moderate level of evidence implicating a negative relationship between cannabis use and motivation. 4/6 (66.7%) of included studies assessing this behavioral sequela observed a negative effect of cannabis use
Psychosocial Functioning (*N* = 8)	There is substantial evidence that daily or weekly cannabis use throughout high school is associated with lower educational and occupational attainment	(106–112)	One study indicated that cannabis use in high school is not associated with educational performance	(98)	There is a strong level of evidence implicating a negative relationship between cannabis use and psychosocial functioning. 7/8 (87.5%) of included studies assessing this behavioral sequela observed a negative effect of cannabis use

(Continued)

TABLE 1 | Continued

Behavioral Outcome Measured	Negative Effects	References	Positive or Neutral Effects	References	Conclusions
Depression (*N* = 27)	There is evidence that daily or weekly cannabis use beginning in adolescence is a risk factor for a diagnosis of major depressive disorder (MDD) in adulthood	(54, 90, 100, 107, 109, 113–123)	Some evidence from case-control designs suggest that cannabis use is not associated with depression and acute administration of THC may decrease depressive symptoms for a short period of time	(51, 61, 124–132)	There is a mixed level of evidence implicating a relationship between cannabis use and increased depression. 16/27 (59.3%) of included studies assessing this behavioral sequela observed a negative effect of cannabis use
Anxiety (*N* = 23)	There is evidence that chronic cannabis use beginning in adolescence and acute, high dose administration of THC is associated with an increase in anxiety symptomology	(13, 14, 41, 52–54, 90, 100, 107, 116, 119–121, 133)	However, there is also evidence that acute, low dosing of CBD is associated with a decrease in anxiety symptomology	(61, 113, 115, 122, 127, 129, 134–136)	There is a moderate level of evidence implicating a relationship between cannabis use and increased anxiety. 14/23 (60.9%) of included studies assessing this behavioral sequela observed a negative effect of cannabis use
Psychosis (*N* = 27)	There is substantial evidence that chronic cannabis use in adolescence and acute, high dose administration of THC is associated with an increased risk for a psychotic disorder or acute psychosis, respectively	(13–15, 24, 53, 54, 93, 107, 124, 132, 137–152)	There is minimal evidence that cannabis is not associated with greater psychotic symptoms	(61, 153)	There is a strong level of evidence implicating a relationship between cannabis use and increased risk for psychosis. 25/27 (92.6%) of included studies assessing this behavioral sequela observed a negative effect of cannabis use

TABLE 2 | The strength of evidence concerning cannabis and cannabinoids in behavioral outcomes among persons without a medical condition or history of a psychiatric disorder.

Behavioral Outcome	Number of studies finding a negative impact of cannabis use	Number of studies finding no impact of cannabis use	Level of Evidence
Verbal, Episodic, and Verbal Working Memory	24	13	**4** (24/37 = 64.9%)
Visuospatial Memory	1	6	**1** (1/6 = 16.7%)
Attention	12	8	**4** (12/20 = 60.0%)
Processing Speed	3	3	**3** (3/6 = 50.0%)
Executive Function	16	8	**4** (16/24 = 66.7%)
Impulsivity/Inhibitory Control	10	7	**3** (10/17 = 58.8%)
Intelligence (IQ)	3	4	**3** (3/7 = 42.9%)
Motivation	4	2	**4** (4/6 = 66.7%)
Psychosocial Functioning	7	1	**5** (7/8 = 87.5%)
Depression	16	11	**3** (16/27 = 59.3%)
Anxiety	14	9	**4** (14/23 = 60.9%)
Psychosis	25	2	**5** (25/27 = 92.6%)

1 = 0–19% corresponds with strong evidence of no effects of cannabis use.
2 = 20–39% corresponds with moderate evidence of no effects of cannabis use.
3 = 40–59% corresponds with mixed evidence of neutral or negative effects of cannabis use.
4 = 60–79% corresponds with moderate evidence of negative effects of cannabis use.
5 = 80–100% corresponds with strong evidence of negative effects of cannabis use.

spontaneous and suggestion-based false memories immediately after intoxication in comparison to placebo. The authors surmise that THC-intoxicated individuals may demonstrate a tendency toward more liberal responding to memory-related questions due to reductions in alertness and impaired abilities in forming learning associations. Additionally, the effects were most prominent at immediate in comparison to delayed recall. One experimental design administering vaporized THC (12%) or placebo to male, recreational, adolescent and adult cannabis users found that in comparison to adolescent users, adults exhibited greater impairments in a spatial working memory task following intoxication (41).

Three experimental designs found no relationship between acute cannabinoid intoxication and memory impairments (14, 61, 70). Bhattacharyya et al. (14) conducted an fMRI studying neurocognitive function during the Hopkins Verbal Learning Task after acute oral THC administration (10 mg) to healthy, occasional cannabis users. Although overall task performance was unaffected, THC attenuated brain activation in regions associated with episodic memory. These findings implicate that greater neural effort is required after THC administration to maintain normal levels of task performance. Additionally, Englund et al. (61) investigated whether a pre-treatment of 10 mg of oral Δ-9-tetrahydrocannabivarin (THCV) prior to 1 mg of THC intoxication would lead to cognitive and clinical effects among a non-clinical sample of men. The authors found that

pre-treatment with THCV protected participants from memory impairments in a delayed memory recall task.

Overall, the literature suggests that acute THC intoxication produces acute impairments in verbal learning, episodic, and working memory. Moreover, the literature suggests a dose-dependent relationship between levels of cannabis use and long-term impairments within this cognitive domain.

Attention

Seven cross-sectional studies found a significant association between cannabis use and attention deficits (36, 40, 46, 64, 73, 74, 77). Fontes et al. (74) compared a sample of adult early-onset (before age 15), late-onset (after age 15), and non-users on a sustained attention task. Results indicated that early-onset users demonstrated significant impairments in comparison to controls and late-onset users. Similar findings were also obtained by Jacobsen et al. (73), where adolescent cannabis users performed significantly worse on a sustained attention task relative to controls and adolescent tobacco users. However, five cross-sectional designs indicated no differences in attention between cannabis users and non-users (44, 48, 57, 66, 78). Fridberg et al. (78) and Jager et al. (57) each investigated whether chronic cannabis users demonstrated impairments in selective attention, both in terms of behavioral performance and abnormal brain activity. Although both studies found that cannabis users performed equally fast and accurate as controls, cannabis users demonstrated abnormal brain activity as evaluated through fMRI and EEG, respectively.

Five experimental designs found that shortly after THC intoxication, adult participants without a medical or psychiatric disorder demonstrated significant deficits in attention (53, 70–72, 76). Desrosiers et al. (70) found that after acute, THC intoxication, recreational cannabis users performed significantly worse on a divided attention task in comparison to chronic users. The researchers surmised that the differences in performance are attributed to tolerance development in frequent smokers. Two major limitations of this study should be noted, however. First, performance while sober was not obtained in the study, so conclusions on overall attention impairments were limited. Additionally, occasional and frequent users' performance was not compared against a group of healthy controls to further evaluate the significance of their impairments. A more recent experimental design compared the effects of THC-dominant and THC/CBD equivalent cannabis ratios among a non-clinical sample on a task of divided attention (72). Unlike prior research (15, 24), the co-administration of CBD did not mitigate any adverse, cognitive effects of THC, and participants demonstrated significant attention deficits in both conditions. However, one experimental design administering either 0.015 or 0.03 mg/kg of THC to former, recreational cannabis users without a medical or psychiatric disorder found no impairments in sustained attention, as measured via the Rapid Visual Processing Task (79).

One longitudinal study following adolescents for 2 years found no relationship between cannabis use and speeded attention (35). However, users did demonstrate impairments in other cognitive domains, including working memory and planning. Rabin et al. (62) compared the effects of extended (28 day) cannabis abstinence and reinstatement of cannabis use in people with schizophrenia and healthy controls with cannabis use disorder and found no improvements in sustained attention among both groups of abstainers. Improvements were not obtained in multiple cognitive domains as well, including executive function and visuospatial working memory.

Overall, the literature suggests a relationship between chronic cannabis use and impairments in attention. However, more evidence is required to ascertain whether there is a dose-dependent effect of levels of cannabis use and deficits in this cognitive domain. Additionally, acute THC-intoxication appears to produce temporary impairments in attention.

Processing Speed

Two cross-sectional studies and one experimental study found a relationship between cannabis use and impairments in processing speed (36, 64, 72). Thames et al. (36) evaluated whether cannabis use in the previous month impacted neurocognitive functioning in a non-clinical adult sample. Participants were classified as either recent users (last use within 4 weeks since study), remote cannabis users (last use >4 weeks since study), and non-users (no report of cannabis use). Recent users demonstrated impairments in information processing speed in addition to other cognitive domains (e.g., attention, working memory, and executive functioning) in comparison to past- and non-users (36). Interestingly, past users did not differ from non-users in any domain except for executive functioning, suggesting that cannabis abstinence can restore previous cognitive abilities. A rigorously controlled experimental design compared whether high THC/CBD vs. equivalent THC/CBD cannabis ratios would produce differential cognitive impairments among volunteers with no history of a psychiatric disorder (72). In an information processing speed task, 1:1 THC/CBD intoxication produced greater impairments in participants in comparison to the high THC/CBD condition, suggesting that CBD may not effectively prevent cognitive impairments associated with THC intoxication.

However, one recent 14 year longitudinal study following adolescents at baseline yearly, determined no relationship between cannabis or alcohol use and performance in tasks evaluating processing speed (63). Furthermore, two cross-sectional designs evaluating processing speed among older adults without a current medical condition or psychiatric disorder, no relationship between cannabis use and this cognitive domain emerged (56, 65). Burggren et al. (65) evaluated verbal memory, processing speed, and executive functioning among a sample of older adults who were former, chronic, cannabis users in addition to non-users and found that while former users performed worse than non-users on all cognitive domains, the differences were not significant. Similarly, Thayer et al. (56) obtained no behavioral differences in processing speed and other cognitive domains across a sample of older adults who were either current, chronic, cannabis users or had no history of cannabis use.

Overall, the evidence remains mixed on whether cannabis use alters processing speed, and whether there is a dose-dependent relationship between cannabis use and impairments in this neurocognitive ability.

Executive Function

Three longitudinal designs implicate a significant relationship between adolescent cannabis use and impairment in executive functioning (35, 47, 86). Castellanos et al. (86) concluded that frequent cannabis use among adolescent boys was associated with a significant decline in executive functioning by the end of high school. The relationship persisted even after controlling for high school graduation and other substance use. Additionally, a more recent longitudinal study obtained similar findings. Becker et al. (35) found that in comparison to adults without a history of cannabis use, chronic cannabis users who began use in adolescence, demonstrated significant reductions in planning and verbal learning at a 2 year follow-up. Additionally, reducing cannabis use did not ameliorate users' cognitive deficits.

Eight cross-sectional designs obtained a significant relationship between cannabis use and impairments in executive functioning (49, 74, 77, 80–83, 85). Four of these studies implicated that chronic cannabis users demonstrate significant impairments in decision-making in comparison to their non-using counterparts (77, 80, 81, 85). Two studies comparing early-onset (use began before age 16), late-onset (use began at or past age 16), and non-using controls in tasks evaluating executive functioning (e.g., Stroop task, Frontal Assessment Battery, and Wisconsin Card Sorting Test) suggested that only early-onset users performed poorly on these tests in comparison to both the late-onset users and healthy controls (74, 82).

However, seven cross-sectional studies found no deficits between cannabis users and non-users on tasks assessing executive functioning (48, 56, 65, 66, 87–89). In a study comparing numerous cognitive abilities between controls and older adults who were currently using cannabis, no differences between groups on any neuropsychological test emerged (56). Furthermore, employing structural MRI, the authors also obtained no significant differences between groups in white or gray matter density. However, one limitation of this study is that duration and levels of use was not specified, which may have impacted the findings. Moreover, employing fMRI, Hatchard et al. (88) obtained no performance differences between cannabis users and non-users on a Counting Stroop Task. However, in contrast to non-users, cannabis users displayed more intensive and extensive BOLD responses. The researchers surmise that the recruitment of additional brain regions among cannabis users may be a neural compensatory strategy to maintain their behavioral performance. Additionally, in one study comparing 25 day abstinent, adult, chronic cannabis users, cocaine users, and non-using controls on the Iowa Gambling Task, cocaine users demonstrated significant learning impairments in comparison to cannabis users and controls (89). Although abstinent-cannabis users did not significantly differ from controls on the task, their performance was consistently lower. This finding implicates that cannabis use may negatively impact executive functioning, but with abstinence, cognitive deficits are somewhat reversible. Finally, the researchers also obtained a dose-dependent effect of cannabis use on IGT performance, which implicates that this substance may affect cognition.

Overall, our review obtained a moderate level evidence concerning the effects of cannabis use and impairments in executive functioning. However, levels of cannabis use did not consistently correspond with greater impairments in this neurocognitive domain.

Impulsivity/Inhibitory Control

Only one longitudinal study investigated the role of cannabis use on the course on inhibitory control (63). Following adolescents between the ages of 12–15 annually, for 14 years, Infante et al. (63) found that greater cumulative cannabis use in adolescence was associated with deficits in inhibitory control in adulthood. The effects remained after controlling for relevant confounders including alcohol use.

Concerning cross-sectional designs, six studies also concluded that cannabis users exhibit greater impulsivity and poorer inhibitory control than non-users (44, 48, 64, 74, 91, 92). Lisdahl and Price (64) examined whether past-year cannabis use among adolescents and young adults corresponded with impairments in inhibitory control. After controlling for numerous confounders, cannabis use corresponded with poorer cognitive inhibition in a dose-dependent fashion. Additionally, there is some evidence that cannabis use corresponds with greater impulsivity in daily life. Ansell et al. (91) employed Ecological Momentary Assessment (EMA) to examine more immediate effects of cannabis on same day and subsequent day reports of impulsivity among a sample of chronic, cannabis-using adults. The authors found that independent of alcohol consumption, cannabis use was associated with same day increases in impulsivity and predicted next day increases in impulsivity.

However, three separate cross-sectional studies reported no impulsivity differences between cannabis users and non-users (38, 94, 95). In a study comparing inhibitory control among 28 day abstinent adolescent cannabis users and non-users, no significant differences between the groups' performance on a go/no-go task emerged (95). Similar findings were obtained by a more recent study, where regular, young-adult cannabis users and matched non-users performed similarly on an inhibitory task (94). However, when the authors compared early-onset (prior to age 16) and late-onset (ages 16 or later) cannabis users, individuals in the former group made greater errors of commission, but the results remained insignificant.

Although the literature is ambiguous on whether cannabis use produces long-term effects on impulsivity, there is evidence that acute administration of THC produces impairments in inhibitory control. Five experimental designs suggest a relationship between THC intoxication and increased impulsivity (41, 71, 76, 90, 93). Employing a double-blind, placebo-controlled design, Ramaekers et al. (71) compared the effects of 500 μg/kg of THC among occasional and chronic cannabis-using adults in the stop signal task (SST) 35 min, 3 h 30 min, 5 h 30 min, and 7 h 30 min post-THC administration. Both occasional and heavy cannabis users demonstrated impaired inhibitory control in the intoxicated condition, where worst performance arose 35 min after intoxication. To replicate this study's findings, Theunissen et al. (76) repeated the former study with a different group of occasional and chronic cannabis users and found that both users

demonstrated significant impairments in the SST 45 min after THC administration.

Overall, whether chronic cannabis use reduces inhibitory control in a dose-dependent manner is less clear. However, the literature suggests that acute administration of THC leads to greater impulsivity and poorer inhibitory control.

Intelligence (IQ)

Six longitudinal studies assessing the impact of cannabis use on IQ were included (42, 47, 86, 97–99). Two cohort studies concluded that there was a significant association between cannabis use beginning in adolescence and a decline in IQ (47, 86). Castellanos-Ryan et al. (86) concluded that frequent cannabis use among adolescent boys is associated with a significant decline in verbal IQ scores by the end of high school. Moreover, the authors found that poor short-term and working memory in pre-adolescence was associated with an earlier age of onset for cannabis use. Despite these findings, the relationship between cannabis use and verbal IQ was mediated by a reduction in high-school graduation rates. Meier et al. (47) conducted a large, national representative, birth-cohort design ($N = 1{,}748$) which explored the relationship between cannabis use from preadolescence into adulthood and potential changes in IQ and cognitive abilities. Individuals who received a diagnosis of cannabis use disorder before the age of 18 demonstrated an eight-point decline in IQ by the age of 38 in comparison to peers who never used cannabis or began use after the age of 18 (47). This relationship persisted after statistically adjusting for alcohol, tobacco and other drug use, schizophrenia, and educational level.

However, four cohort designs assessing cannabis use and IQ changes indicate that there is no direct relationship between these two variables (42, 97–99). In a birth-cohort twin study, adolescent cannabis use was associated with a decline in IQ and impaired executive functioning, but twins who used cannabis performed no worse than their co-twin without a history of cannabis use (42). The authors subsequently suggest that family background factors contribute to a spurious relationship between cannabis use and impaired executive functioning in the general population. An additional, cohort, twin design also indicated no relationship between cannabis use and IQ decline (99). Participants' IQ was measured prior to cannabis use between the ages of 9 to 12 years old, and again 8 years later. Cannabis use between this period corresponded with reduced scores in IQ at follow-up, however no clear relationship between frequency of use and IQ emerged. Consequently, the authors determined that the declines in IQ reflected the effects of familial or genetic factors that predated cannabis use onset. In a separate study investigating cognition and verbal IQ among 28 day abstinent early-onset (smoking before age 17) cannabis users, late-onset (smoking at or after age 17) cannabis users, and controls, only early-onset users performed poorly on measures evaluating verbal IQ (55). However, this relationship did not persist after controlling for relevant variables, including familial and childhood factors.

Currently, the literature remains mixed on whether chronic cannabis use impacts intelligence and IQ. Some studies suggest that there is a dose-dependent relationship between cannabis use and IQ scores, while other evidence suggests that there is no relationship between these variables.

Motivation

Four cross-sectional studies included in the review implicate that cannabis users demonstrate motivation impairments in comparison to non-users (100–103). In a study examining the influence of reward on mood and performance on the spatial delayed response task in an adult sample of chronic cannabis users, tobacco smokers, and non-smoking controls, cannabis users rated their mood as significantly lower than smokers and controls during the reward conditions (101). The authors concluded that cannabis use may reduce reward processing at a behavioral level. Additionally, Lane et al. (103) found that on a monetary task assessing perseverative responding, adolescent cannabis users switched to the non-work, but less rewarding task significantly earlier than non-users.

However, two cross-sectional studies obtained no relationship between cannabis use and reductions in motivation (104, 105). In one study comparing adolescent cannabis users and non-users on a self-report battery examining high school students' motivation, no differences emerged (105). Additionally, Jager et al. (104) compared the performance of abstinent cannabis-using boys and non-using boys on the monetary incentive delay (MID) task, which assesses motivation and reward processing. Although no behavioral differences between groups emerged, a significant limitation of the study should be noted. Cannabis abstinence was not controlled for and varied from 1 to 16 weeks, which may have impacted the observed findings. Overall, the evidence suggests a dose-dependent relationship between cannabis use and impairments in motivation.

Psychosocial Functioning

We identified eight longitudinal studies demonstrating that cannabis use has adverse effects on psychosocial functioning, including occupational and educational attainment (86, 106–112). Follow-up times ranged from 1 to 35 years. One study using a large, nationally representative sample found that among students from grade 9–12, individuals who used cannabis at baseline were less likely to attend class, complete their homework, and obtain or value high grades relative to their abstaining peers at year 2 and 3 (111). Furthermore, frequent cannabis use reduced the likelihood of planning to pursue either a graduate or professional degree post-graduation. A recent birth cohort study assessed four trajectories of cannabis use, including non-users, adolescent-limited, adult-onset, and chronic-adolescent users (107). Individuals who began cannabis use in adolescence and continued use throughout adulthood demonstrated the worst psychosocial functioning at age 35, while the non-user group reported the highest level of well-being. Moreover, heavy cannabis use in adolescence corresponded with an increased risk of adverse outcomes at ages 30–35, including a reduced likelihood to attain a postsecondary degree, a lower weekly income, a greater likelihood to rely on welfare, a greater likelihood of being unemployed, and a greater likelihood of being arrested. In contrast, one prospective, cohort design concluded that although there was a significant relationship between cannabis use at age 15

and educational performance at age 16, this relationship became non-significant after adjusting for relevant variables such as cigarette smoking, childhood conduct problems, and childhood depressive symptoms (98).

Overall, the evidence obtained in this review implicates a dose-dependent relationship between levels of cannabis use and poorer psychosocial outcomes.

Depression

We identified two experimental studies demonstrating a negative effect of THC in mood among a group of adults without a history of medical or psychiatric illness (15, 122). In one study, male participants received 10 mg of THC and reported their mood 1, 2, and 3 h post- THC administration. Relative to placebo, participants reported significantly elevated levels of dysphoria (15). However, two separate experimental studies administering THC to a non-clinical sample did not obtain similar findings (51, 61). Instead, both studies found that there was a dose-dependent relationship between THC consumption and pleasurable mood ratings.

Concerning longitudinal findings, we identified thirteen studies that suggested a relationship between cannabis use and a greater likelihood of developing major depression (107, 109, 113–121, 123, 131). However, six of these studies specifically outlined that only heavy or chronic (<4 times/week) adolescent cannabis use is a risk factor for depression in adulthood. Otten and Engels (123) investigated the relationship between cannabis use, depression, and the serotonin transporter gene (5-HTTLPR). The serotonin transporter gene is considered a significant candidate gene for its role in depression [for a review, see (154)]. Specifically, this gene encodes the serotonin transporter protein, which is responsible for the reuptake of serotonin from the synaptic cleft into the presynaptic neuron. The authors identified that cannabis use increases the risk for an increase in depressive symptoms over a 5 year period but only in users with the short allele of the 5-HTTLPR genotype. One study also investigated whether sex differences emerged when evaluating the effect of adolescent cannabis use and depressive symptomology in young adulthood (121). A state-wide secondary school sample of 1,601 students aged 14–15 were followed for 6 years. Daily use in female adolescents was associated with a 5-fold increase in the odds of reporting depression and anxiety after adjustment for concurrent use of other substances. Weekly or more frequent cannabis use in adolescents predicted an ∼2-fold increase in risk for later depression and anxiety at follow-up, even after adjusting for potential confounders.

However, 10 separate cohort designs suggest that cannabis use is not associated with an increased risk of a future depression diagnosis (124–132, 155). Despina et al. (125) assessed 1,606 adolescents and obtained data on frequency of cannabis use and serious suicidal ideation at ages 15, 17, and 20 years. While cannabis use did not predict depressive symptomology or suicide ideation, depression predicted subsequent cannabis use, even after adjusting for possible confounders, including other substance use. Additionally, it is important to note that five of these longitudinal designs only considered adult cannabis use at baseline, which limited conclusions concerning the causal relationship between adolescent cannabis use and subsequent depressive symptomology (124, 126, 127, 131, 155).

Three cross-sectional designs also concluded that relative to non-users, cannabis users had more severe depressive symptomology (54, 100, 102). Employing positron emission tomography (PET), Bloomfield et al. (102) evaluated the relationship between dopaminergic function and subjective apathy in a sample of adult, chronic cannabis users. In comparison to normative data from adult without a history of cannabis use, cannabis users reported significantly greater levels of apathy and demonstrated reduced dopamine synthesis capacity.

Overall, the evidence obtained is mixed regarding the impact of cannabis use on depressive symptomology. Some studies suggest a dose-dependent relationship between levels of cannabis use and increased risk of depression, while other evidence found no relationship between these variables after controlling for relevant confounds.

Anxiety

Three prospective cohort designs implicate cannabis use as a significant risk factor for subclinical anxiety symptomology (116, 119, 133). One longitudinal study determined that among adolescent boys, increases in past-year cannabis use corresponded with increases in depressive and anxious symptomology the following year (119). Similarly, Hayatbakhsh et al. (116) found that after controlling for numerous confounding variables, cannabis use before the age of 15 correlated with greater anxious symptomology at age 21 among a national representative sample of adolescents ($N = 3{,}239$).

Four prospective designs suggest chronic cannabis use as a significant risk factor for the development of an anxiety disorder (107, 120, 121, 133). A birth-cohort study collecting information until participants reached 21 years old determined that frequent cannabis use in adolescence predicted a more than 2-fold increase in the diagnosis of an anxiety disorder by the final follow-up (133). This relationship persisted after controlling for tobacco, alcohol, and other substance use. Additionally, anxiety symptomology never predicted subsequent cannabis use. An additional birth-cohort longitudinal design investigated the impact of cannabis use and internalizing problems until age 35 (107). Adolescent-onset cannabis users and young-adulthood cannabis users were significantly more likely to be diagnosed with an anxiety disorder in comparison to adolescent-limited cannabis users, and non-users. The effect persisted even after controlling for childhood, other substance use, and familial factors. Additionally, one cohort study following a group of 14 year-olds for 15 years obtained no consistent relationship between adolescent cannabis use and a diagnosis of major depressive disorder at 29, but daily cannabis use in adolescence was a significant risk factor for development of generalized anxiety disorder at 29, even after adjusting for baseline confounders and other concurrent drug use (120). The researchers also found that overall, among participants, there was a reduction in cannabis use over young adulthood.

However, among individuals who developed an anxiety disorder, the pattern of use was associated with either the maintenance or increasingly frequent use of cannabis throughout young adulthood. Despite these findings, six prospective studies obtained no relationship between cannabis use and an increased risk for a diagnosis of an anxiety disorder or an increase in subclinical anxiety symptomology (113, 115, 127, 129, 135, 155). One UK birth cohort study investigated the relationship between cannabis or cigarette use (at age 16) and diagnosis of depression or anxiety 2 years later (115). The authors determined that after adjusting for potential confounds and cigarette use, the relationship between cannabis use and anxiety symptomology diminished to a non-significant result. Similarly, in another population-based cohort design spanning 30 years, cannabis use in adolescence predicted depressive symptomology and suicidality at age 50, but not anxiety (113). Two other prospective cohort designs also determined that cannabis use in adulthood was not associated with anxiety symptomology, however these studies did not obtain or consider information regarding adolescent cannabis use (127, 135).

Two cross-sectional designs comparing non-clinical cannabis users to non-users suggested a relationship between cannabis use and greater subclinical anxiety symptomology (54, 100). One study classified cannabis users into those demonstrating presence of CBD in hair and those who did not, in addition to high- or low- THC levels. Users with high-THC levels in their hair and users with no CBD reported the most depressive and anxious symptomology, suggesting negative long-term effects of high-THC on mood (54). Wright et al. (100) investigated whether adult, non-clinical cannabis users differ from non-users in self-reports of anxiety, depression, and behavioral approach to rewards. In line with their hypothesis, users reported elevated depressive symptoms, and female users reported elevated anxiety symptoms than non-users.

Seven experimental studies in which healthy non-users received varying doses of THC produced greater anxious symptomology in comparison to placebo (13–15, 41, 52, 53, 90). McDonald et al. (90) administered either 7.5 or 15 mg of THC to a sample of men and women with no history of a psychiatric disorder prior to a neurocognitive battery and found a dose-dependent effect of THC on anxiety, anger, fatigue, and confusion. A more recent study provided recreational cannabis users either placebo (0 mg), 29, 49, and 69 mg of THC and obtained a dose-dependent effect of THC on increasing levels of anxiety (52). Additionally, the researchers found that subjective effects persisted up to 8 h post-intoxication.

Finally, two studies administering THC to volunteers without a history of a psychiatric disorder found no effects of THC on anxious symptomology while an additional two studies suggested an anxiolytic effect of CBD among a sample of healthy participants (61, 122, 134, 136). Zuardi et al. (136) and Linares et al. (134) both found that 300 mg of CBD reduced adult participants' self-report of speech-induced anxiety in comparison to placebo, 150 or 600 mg of CBD.

Overall, the literature implicates a dose-dependent relationship between greater levels of cannabis use and elevated anxious symptomology. However, the evidence suggests acute, anxiolytic effects of CBD, a constituent of cannabis sativa.

Psychosis

Thirteen longitudinal designs concluding a relationship between cannabis use and an increased risk for the development of a psychotic disorder were included in this review (124, 132, 138, 141–144, 147–152). One cohort study following Swedish male conscripts at ages 18–20 for 27 years obtained a dose-dependent relationship between cannabis use and a formal diagnosis of schizophrenia (143). However, the study was limited in that data regarding use of cannabis before conscription was unavailable. A more recent, nationally representative, birth cohort design ($N = 6{,}534$) also identified a dose-dependent, positive relationship between adolescent cannabis use and psychosis in adulthood (151). Cannabis use between the ages of 15–16 years was associated with a subsequent psychosis diagnosis by age 30, and this effect persisted after controlling for baseline prodromal symptoms, daily smoking, alcohol use, other substance use, and parental psychosis. A separate cohort design found that cannabis use at age 16 predicted psychotic symptoms at age 19 (152). However, psychotic symptoms at age 13 predicted cannabis use at, respectively, ages 16 and 19, providing support for a bidirectional causal association between the two variables. Only one cohort design did not obtain a significant relationship between cannabis use and an increased risk for psychosis after adjusting for relevant confounders, including tobacco use (153).

Two cross-sectional studies comparing cannabis users and non-users without a psychiatric disorder concluded that users report greater psychotic symptoms than non-users (54, 137). Morgan et al. (54) classified cannabis users via hair samples into those who use both THC and CBD, and those who only use THC. Cannabis users who only demonstrated use of THC reported significantly more psychotic symptomology than THC and CBD users and non-users, implicating a relationship between THC and psychotic symptomology. Similarly, a more recent cross-sectional design attained a dose-dependent relationship between cannabis use frequency and severity of psychotic symptoms including mania, paranoia, and presence of auditory hallucinations (137). The effects persisted even after adjusting for relevant confounds, such as sex, age, and other substance use (137).

One pilot, within-subjects, placebo-controlled, double-blind design obtained no effect of acute THC administration on psychotic, anxious, or depressive symptomology following a 5 day pre-treatment of THCV (61). An earlier study led by the same team of researchers also found that pre-administration of CBD reduced participants' self-reports of psychotic symptomology on the Positive and Negative Affect Syndrome Scale (PANSS) (140). However, relative to placebo, this difference did not reach significance, suggesting that CBD may not fully attenuate the psychotic symptoms produced by THC.

Overall, the literature presents strong evidence that acute THC intoxication increases reports of psychotic symptomology. Moreover, the literature suggests a dose-dependent relationship between levels of cannabis use and increased risk for the development of a psychotic disorder.

DISCUSSION

Cognition

Concerning cognitive impairments, there is moderate evidence that chronic cannabis use and acute THC intoxication may negatively impact verbal, working, and episodic memory, executive functioning, and divided and sustained attention in users. However, cannabis does not appear to affect all cognitive domains, as impairments in visuospatial memory, processing speed, inhibitory control, and IQ were less consistent with mixed results.

Our review suggests a dose-dependent relationship between chronic cannabis use and verbal, episodic, and working memory impairments, but primarily among individuals who began use in adolescence. These findings coincide with preclinical animal models which have found that repeated exposure to THC during adolescence, but not adulthood, negatively impacts multiple cognitive domains, including memory, throughout the lifespan (156, 157). We also found modest evidence for improvements in cognition with cannabis abstinence, as some studies comparing non-users and past users demonstrated similar levels of performance among laboratory assessments (36, 65, 66). Given the brain's plasticity, restoration of neurocognitive abilities may be expected. A recent meta-analysis investigating residual cognitive impairments in cannabis users found no significant deficits among individuals who had abstained for at least 25 days (158). However, additional well-controlled prospective designs monitoring cognition from current use through cessation of use and over extended periods of abstinence are needed.

Among studies investigating the effects of acute THC administration, the evidence implicates greater impairment in cognition among recreational cannabis users and non-users in comparison to chronic cannabis users [e.g., (48, 61, 70, 79)]. In fact, a recent review evaluating the development of tolerance among cannabis users obtained comparable findings suggesting that cognition was most impaired upon acute THC intoxication (159), suggesting minimal tolerance.

Despite these findings, mixed evidence for numerous cognitive domains in this review arose, which may be due to variability in the control variables employed, cognitive tests utilized, operationalization of cognitive domains, participants' cannabis use histories, and cannabis exposure heterogeneity. Irrespective of these limitations, the effects obtained in this systematic review suggest that impairment of numerous cognitive domains can persist well-beyond the period of acute intoxication and consequently adversely impact everyday functioning in cannabis users.

Motivation

Although the research concerning the effects of cannabis on motivation among non-clinical populations is limited, the evidence suggests a moderate negative relationship between cannabis use and motivation. These findings align with the "amotivational syndrome," a term first coined by Smith [(160), p. 43] which purports that individuals who use cannabis are characterized by "a loss of desire to work or compete", in addition to reduced emotional reactivity and interest in attaining goals (161).

While cannabis use may adversely impact motivation, the results need to be interpreted with caution due to certain methodological limitations. All of the included studies were cross-sectional, which significantly limits our understanding concerning the directionality between these two variables. Moreover, the conception and operationalization of motivation greatly differed across studies. While some of the included studies employed self-report measures such as the Apathy Evaluation Scale (AES) to measure apathy, other studies utilized performance-based tasks and operationalized motivation as perseverance in working for a monetary reward. Despite these methodological limitations, the evidence concerning cannabis use and reduced motivation aligns with studies suggesting that chronic cannabis users demonstrate reduced occupational and educational attainment compared to non-users [e.g., (107, 111, 112)]. Nevertheless, the field can significantly benefit from controlled, large-scale prospective designs evaluating motivation throughout the life trajectory while considering the impacts of the frequency of cannabis use, age of onset for use, and the influence of other substance use on motivational outcomes.

Psychosocial Functioning

With a global trend toward legalization and decriminalization of cannabis for medical and/or recreational uses, the potential psychosocial harms accompanying cannabis use remain a major public health concern. Use of cannabis by adolescents is widespread and our findings suggest that chronic cannabis use throughout this developmental period is strongly associated with reduced educational and occupational attainment among this population. Nevertheless, the mechanisms linking cannabis and educational and economic risks are unclear. However, early age of onset, frequent or heavy use, and predictors of early use (e.g., childhood conduct or depressive symptoms), may undermine educational and occupational attainment. Consequently, delaying use onset and reducing the frequency of cannabis use patterns among adolescents may be beneficial in minimizing disruptions to educational goals and economic success.

While much of the evidence focuses on post-secondary or high school educational attainment, only one study included in the review followed a birth cohort until middle adulthood (107). The authors found that persistent cannabis use throughout adulthood corresponded with adverse mental health, substance use, and psychosocial outcomes, even after controlling for relevant confounding factors. Moreover, the authors denoted individual and childhood factors predicting persistent cannabis use in adulthood, including novelty-seeking, parental substance use, deviant peer affiliation, and conduct disorder diagnosis in adolescence. While additional, well-controlled studies are required to substantiate these findings, regardless of causality, our review indicates that individuals who utilize heavy amounts of cannabis for an extended period may experience adverse consequences to their social and economic well-being throughout the lifespan.

Psychiatric Outcomes

Depression and Anxiety

The review obtained mixed evidence concerning the relationship between cannabis use and depressive symptomology. Numerous studies implicated a dose-dependent relationship between cannabis use beginning in adolescence and increases in depressive symptomology. However, this effect was inconsistent across studies, which may be attributed to methodological differences within the literature. For example, differences surrounding the follow-up period and assessments of cannabis use frequency and levels may have precluded other authors from distinguishing a relationship between cannabis use and depressive symptomology. Moreover, the reported association between cannabis use and depression may have been influenced by variation among the controlled variables across the studies reviewed. A modest proportion of the cohort studies obtaining a significant relationship between adolescent cannabis use and increased depressive symptomology in adulthood did not account for additional substance use, such as nicotine and alcohol [e.g., (117, 118)]. This is of significance because alcohol and tobacco use are prevalent among cannabis users, and these substances may independently elevate individual susceptibility to depression if used throughout adolescence (162–164).

Concerning the effects of cannabis use on anxious symptomology, while individuals frequently report cannabis as an effective agent to relieve anxiety, [e.g., (165)] the evidence suggests a moderate dose-dependent relationship between cannabis use and heightened anxious symptomology. One potential exception surrounding these findings is in the case of cannabidiol (CBD). Among two randomized, double-blind, placebo-controlled, experimental designs, relative to placebo, CBD reduced anxiety on a social stress test among a sample of non-clinical participants (134, 136). While these findings implicate an anxiolytic effect of CBD, future research is necessary to evaluate whether these effects persist long-term.

Despite these findings within the anxiety literature, there are some noteworthy methodological considerations. Similar to the findings surrounding cannabis and depression, controlled factors varied across studies. Several cohort designs did not obtain significant relationships between cannabis use and anxiety disorders after controlling for other substance use and childhood psychosocial variables [e.g., (117, 127, 135)], while studies that did not control for one or more of these variables did obtain significant findings [e.g., ((63, 129)]. Secondly, follow-up times of cohort designs significantly varied, ranging from 1 to 35 years, with attention directed toward adolescents and young adults. Consequently, the effects of cannabis use on anxious symptomology during middle and late adulthood are poorly understood.

Although the review suggests cannabis as heightening anxious symptomology and possibly depressive symptomology, the mechanism underlying this relationship has not been clearly established. A neurobiological explanation has been put forward suggesting that THC may perturb endocannabinoid system CB1 receptor signaling, which has been linked to psychopathology and dysregulation of emotional experiences (166). Animal models have also demonstrated that administering THC during adolescence elevates symptoms reflecting anhedonia and anxiety in adulthood and is paralleled by neurotransmitter changes, including a diminution in serotonin, which is a neurotransmitter linked to depression, and increases in norepinephrine, which is a neurotransmitter linked with anxiety (167, 168). Interestingly, a recent preliminary study of 28 days of cannabis abstinence in people with major depression and cannabis use disorder suggests clinically relevant improvements in depression, anxiety and motivation (169).

A second explanation for the relationship between cannabis and elevated anxious and depressive symptomology utilizes a psychosocial lens (170). Cannabis use is associated with numerous adverse psychosocial outcomes, including unemployment, increased affiliation with deviant peers, and poorer educational outcomes (106, 112), which are all factors that may increase risk of developing an anxious or depressive disorder.

Psychosis

We found a strong relationship between chronic cannabis use and an increased risk for psychosis. This relationship persisted independent of alcohol [e.g., (143, 153)] and tobacco [e.g., (124, 138, 152)] use. In comparison to non-users, cannabis users have an earlier age of onset of psychotic disorders (143, 147, 151). Moreover, the association between cannabis use and psychotic symptomology is elevated with heavier, more frequent, and earlier use (27, 132, 138, 143). These findings coincide with a large meta-analysis which analyzed over 20,000 subjects, and found that the onset of psychosis is 2.7 years earlier in cannabis users than in non-users (171).

Although the evidence supports a relationship between cannabis use and psychotic symptoms, these findings may be confounded by tobacco use, as a significant proportion of cannabis users also smoke cigarettes. Moreover, many longitudinal studies observing a relationship between cannabis use and increased psychotic symptomology or a diagnosis of a psychotic disorder, had not recorded tobacco use [e.g., (138, 144, 148)]. A recent meta-analysis found that daily tobacco use correlates with an increased risk of psychosis, in addition to an earlier onset of a psychotic disorder (172). However, other evidence suggests that acute nicotine or tobacco use does not exacerbate the positive and negative symptoms of psychosis in schizophrenia [e.g., (173, 174)], and that abstinence does not alter schizophrenia psychosis (175).

Despite the potential confounding role of tobacco use in longitudinal designs, direct evidence obtained within experimental studies demonstrate a clear temporal association between THC-intoxication and increased psychotic symptomology, including positive, negative, and cognitive symptoms [e.g., (24, 53, 146)]. Further, reports of psychosis within randomized, placebo-controlled, experimental studies of THC administration are commonly made, and among some individuals, psychosis persists beyond the acute intoxication phase (15, 176, 177). Therefore, the primary symptom clusters present in schizophrenia are also frequently present in varying degrees during THC-intoxication.

Overall Strengths and Limitations

One of the major strengths of this review includes its behavioral focus: we addressed important questions concerning the clinical, cognitive, and psychosocial outcomes associated with cannabis use. Our findings provide evidence that there are numerous risks associated with cannabis use, which is likely of significant interest to public health officials, educators, policymakers, researchers, healthcare practitioners, and the general public. Additionally, extending our review to a broad array of outcomes allowed us to detect major gaps in the current literature. A final strength of this review is that we employed a methodologically rigorous and comprehensive approach in collecting our evidence by following PRISMA guidelines (32).

Although we performed a comprehensive, systematic review, there are important limitations to note. As previously discussed, many of the studies across the investigated domains did not control for important confounding factors such as alcohol, tobacco and other substance use, or familial and other psychosocial variables [e.g., (58, 63, 74, 129)]. Accordingly, the possibility that the negative impacts of cannabis use upon the outcomes explored are attributed to confounding factors cannot be dismissed. An additional limitation of the present systematic review is the heterogeneity of the included studies insofar as study methodology, outcome measures assessed, and duration of follow-up. Participants differed on various socio-demographic characteristics and cannabis use parameters, including age of onset, lifetime use, abstinence periods for former users, and frequency of use. Moreover, the potency of cannabis used, and relative concentrations of THC and CBD are also important to consider and were infrequently discussed in the included studies. These methodological differences have likely contributed to the mixed findings, and should be addressed in future research.

Despite these limitations, we did identify a trend where frequent or heavy cannabis use in adolescence was typically a significant risk factor for numerous adverse outcomes in adulthood, including worsened educational attainment, reduced IQ, and the development of an anxiety disorder, major depressive disorder and psychosis (See **Table 2** for a summary of the quality of the evidence).

Our findings suggest that the adolescent brain is especially vulnerable to the effects of cannabinoids (especially THC) in comparison to the adult brain. Prior research has demonstrated that exposure to endogenous cannabinoids modifies the endocannabinoid system, which is a major player in shaping neurodevelopmental processes, including modulating neuroplasticity and regulating synaptic connections (178–180). It is possible that cannabis use during adolescence disrupts these neurodevelopmental processes. Consequently, this may produce enduring changes in brain structure and function that underlie many of the adverse cognitive and clinical outcomes associated with adolescent cannabis use.

CONCLUSION AND FUTURE DIRECTIONS

The use of cannabis is extensive, ranging from occasional use to daily use and CUD. Although the desired effects sought by recreational cannabis users include relaxation, euphoria, and decreased anxiety, our review obtained evidence of adverse, acute and chronic sequelae of cannabis use, including impairments in cognition, increased risk for psychosis, depression, and anxiety, and poorer psychosocial functioning.

Although the evidence obtained in this systematic review implicates numerous adverse consequences of cannabis use beginning in adolescence, cannabis use among this age group is increasing (5, 181, 182). Moreover, with Canada's recent legalization of recreational cannabis and as more US states (now 10 states plus the District of Columbia) and nations consider legalizing medical or recreational cannabis use, the perceived risk of cannabis has also been trending downward cite (6, 183). Consequently, further investigation of the effects of these policies on usage patterns and related outcomes are a major public health concern.

Future research investigating the impact of cannabinoids during aging processes in middle and late adulthood is strongly needed, as little attention has been paid to this demographic. This is of concern because cannabis use is also increasing among this population (184), yet the effects of this substance in late adulthood are unknown. These studies will be crucial in depicting a more complete picture concerning the replicability and robustness of observed effects.

Finally, our work highlights a clear need for well-controlled longitudinal cohort and experimental vs. cross-sectional designs that utilize standardized measures of cognition, intelligence, motivation, psychiatric symptoms, and psychosocial functioning. Future studies should also be of adequate duration to assess cannabis and constituent effects, and have adequate follow-up periods to evaluate cannabis abstinence effects on these outcome measures. This would permit more accurate measurement of cannabis-related effect sizes on these outcomes. Such refinements in future methodologies would allow rigorous meta-analyses of cannabis effects on these various behavioral sequelae which may ultimately inform clinical and political decision-making.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MS and TG conceived and designed the presented idea. MS and RB were involved in collecting data and designing the tables. MS wrote the manuscript with support from TG. TG encouraged MS to investigate specific topics for the review and supervised the findings of this work. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.630247/full#supplementary-material

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Do Cannabis Users Reduce Their THC Dosages When Using More Potent Cannabis Products? A Review

Janni Leung[1,2]*, *Daniel Stjepanović*[1], *Danielle Dawson*[1,2] *and Wayne D. Hall*[1]

[1] National Centre for Youth Substance Use Research, The University of Queensland, St Lucia, QLD, Australia, [2] School of Psychology, The University of Queensland, St Lucia, QLD, Australia

Background: Higher potency cannabis products are associated with higher risks of negative physical and psychological outcomes. The US cannabis industry has opposed any restrictions on THC levels, arguing that people titrate their THC doses when consuming higher potency products.

Objective: To review research on the degree to which people who use cannabis for recreational purposes can and do titrate their THC doses.

Method: A systematic search was conducted for studies published from 1973 to 2020. We included (1) experimental laboratory studies on dose titration of cannabis products that varied in THC content; (2) observational studies on the use of more potent products; and (3) surveys on whether cannabis users titrate when using more potent products.

Results: In some experiments, there were inverse associations between the THC content and the amount smoked and smoking topography, while others indicated higher doses consumed and psychological and physiological effects observed. Findings of observational studies of regular cannabis users were more equivocal. In some surveys, cannabis users reported that they use less when using more potent products, but in other surveys, persons who used more potent cannabis had more adverse effects of use.

Discussion: There is some evidence from experimental studies that people who use higher potency cannabis for recreational purposes can titrate their THC doses, but less evidence that regular cannabis users do in fact do so. We need much better experimental and epidemiological research to inform the design of regulatory policies to minimize harms from the use of high THC cannabis products.

Keywords: cannabis, marijuana, titration, THC concentration, dose

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Johns Hopkins Medicine,
United States

***Correspondence:**
Janni Leung
j.leung1@uq.edu.au

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INTRODUCTION

In some states in the USA, the legalization of cannabis for adult and medical use has increased the availability and sales of cannabis products, such as extracts, that have a THC content >70% (1). The cannabis industry has resisted proposals to cap THC content by arguing that people who use high potency cannabis extracts titrate their doses (e.g., reduce their THC dosage of higher potency cannabis products to achieve the same desired psychoactive effects). They may, for example, reduce

the amount smoked when using high THC products. They may also inhale smaller puffs or do so less often when using higher potency products (2). The ability to do so will depend upon users understanding the relationship between product potency and their desired effects so that they can titrate their THC dose (3).

We systematically reviewed evidence on the degree to which people who use cannabis for recreational purposes can and do reduce their THC dose when using more potent products.

METHODS

Eligibility Criteria

We included original studies published from 1973 to the date of our search (17 June 2020) if they reported quantitative data on behavior indicative of titrating THC doses from cannabis products (*via* any route of administration) that varied in THC content (e.g., by varying or controlling the amount rolled, inhaled, or consumed).

We excluded studies of medicinal cannabis use and clinical/pharmacological studies where patients/participants were instructed to titrate their dose of cannabis consumption. Our review aimed to examine evidence on recreational cannabis use in non-supervised settings to better inform public health policy on the regulation of recreational cannabis use.

Search Strategy

The search was conducted in PubMed and Embase with terms related to "Cannabis" AND 'Titration' in the title/abstract/related MeSH and Emtree explosion subject headings, with the "Humans" filter applied, as follows:

PubMed search: ((cannabis [tiab] OR marijuana [tiab] OR Cannabis [MeSH] OR Marijuana Use [MeSH] OR Marijuana Smoking* [MeSH])) AND ((titration [tiab] OR self-titration [tiab] OR self-titrating [tiab] OR self-titra* [tiab] OR titrant [tiab] OR titrat* [tiab] OR auto-titration [tiab] OR autotitration [tiab])) AND (humans[Filter]).

Embase search: (((cannabis:ti,ab OR marijuana:ti,ab OR "cannabis"/exp OR "marijuana use"/exp OR "marijuana smoking*") AND (titration:ti,ab OR "self-titration":ti,ab OR "self-titrating":ti,ab OR "self titra*":ti,ab OR titrant:ti,ab OR titrat*:ti,ab OR "auto titration":ti,ab OR autotitration:ti,ab)) AND "human"/de) AND ("article"/it OR "article in press"/it OR "review"/it).

The supplementary search involved the authors' collection and a snowball search of secondary references identified from all relevant records from the database search and authors' collection. Two researchers carried out the screening, study selection, and data extraction.

Synthesis of Results

Findings from experimental and observational studies and surveys were synthesized narratively on evidence of: (1) titration behavior (e.g., amount smoked, smoking topography) and (2) evidence of effective titration, defined as adjusting consumption when using high THC products to deliver the same THC dose or to achieve the same physiological, neurobehavioral, or psychological effects obtained from using a lower dose product.

RESULTS

Study Characteristics

We identified 197 records from the database search and 338 records from the supplementary search, from which, we screened 497 unique titles after exclusion of duplicates. After full-text screening ($n = 81$), we included 15 articles (**Supplementary Figure 1**).

Most studies were from the USA ($n = 9$), with smaller numbers from the UK ($n = 1$) (4), Canada ($n = 2$) (5, 6), and the Netherlands ($n = 3$) (2, 7, 8). Five studies were published after 2010 (2, 4, 9–11).

Experimental laboratory studies (**Table 1a**) recruited young volunteers who were experienced cannabis users and asked them to smoke cannabis that varied in THC concentration (e.g., (9, 10)). Observational studies (**Table 1b**) examined the cannabis use behavior of users (2, 4). Surveys of cannabis users (**Table 1c**) asked users whether they varied their patterns of use when using more potent cannabis products/assessed whether their reports of adverse effects of cannabis varied with the potency of the cannabis products that they used.

Narrative Review

Experimental Laboratory Studies

There was mixed evidence of titration in experimental studies that were conducted in the 70–90's (5, 6, 12–17). These studies used various methods to measure dose titration (e.g., measuring the total amount of THC that was self-administered and assessing the physiological, and psychological effects of the cannabis consumed).

Some of these studies reported differences in smoking topography, such as taking smaller puffs, smaller inhalation volumes, shorter puff duration, longer inter-puff intervals, when using more potent cannabis products (6, 13, 16). Other studies did not (5, 12, 15). The participants in the higher dose conditions in all studies consumed more THC and reported more psychoactive effects, regardless of adjustments in their smoking behavior.

More recent studies have found some evidence of titration. Hartman et al. conducted an experimental study that evaluated the cannabinoid levels in blood and plasma after the use of vaporized cannabis that varied THC content, with and without alcohol consumption, while allowing *ad-libitum* consumption (9, 10). They recruited 32 participants who had used cannabis in the past 3 months no more than three times a week. Nineteen (59%) completed all the sessions and provided data on cannabinoid levels in blood and plasma concentrations (10) and oral fluid (9). Participants inhaled vaporized cannabis (ground cannabis obtained through NIDA) *ad-libitum* for 10 min. The THC levels were 0.008% in the placebo, 2.9% in the low and 6.7% in the high concentration cannabis conditions. Participants consumed the three cannabis products with and without a concurrent low-dose alcoholic beverage, across six testing sessions.

TABLE 1 | Summary of experimental (a), observational (b), and survey (c) studies on titration of recreational cannabis products by potency.

First author (year published), study location	Study design (sample size)	Sample characteristics	Cannabis products examined	Titration measure	Summary of findings	Evidence of titration behavior	Evidence of effective titration[†]
(a) Summary of experimental studies on titration of recreational cannabis products by potency							
Cappell et al. (5), Canada	Experimental, in lab, ($N = 12$)	Experienced in cannabis use, aged 21–28, males	0.8 vs. 0.4% or 0.2% THC flower (as cigarettes)	Total time with smoke in lungs, number of puffs, mean duration of puff, mean interval between puffs, estimated weight of material consumed, finger pulse, blood pressure, and conjunctival injection. Behavioral tasks: pursuit rotor, verbal memory, and raw reaction time.	Effective titration of intake did not occur. Number of puffs and duration for which puffs were held in lungs did not differ as a function of THC concentration. The greater the potency of the products, the more total THC participants consumed.	No	No
Cappell and Pliner (6), Canada	Experimental, in lab, ($N = 60$)	Frequent or infrequent cannabis use, aged 18–29 (mean = 22), males	1.45 vs. 0.73% or 0.36% THC flower (as cigarette)	Cigarette size (small and large), pulse rate, number/duration/intervals between inhalations.	There was some evidence of titration behavior with the amount of cannabis consumed increasing as potency decreased. Participants in the more potent conditions, however, self-administered more total THC, attaining the same subjective endpoint of intoxication.	Yes	No
Domino et al. (12), USA	Experimental, in clinic, ($N = 30$)	Experienced in cannabis use, aged 21–33, males	2.9 vs. 0.5% (as cigarette)	Amount of cigarettes smoked/THC concentration; effects on size of palpebral fissure and pupil diameter; patellar reflex and heart rate; mood as assessed by Clyde Mood test scores.	After being asked to smoke as much as they could, participants in the higher concentrate condition had a higher increase in the amplitude of the patellar reflex and heart rate, blood pressure, pulse rate changes, and on self-reported mood.	No	No
Perez-Reyes et al. (13), USA	Experimental, in lab, ($N = 6$)	Experienced in cannabis use, aged 23–36, 50% males	2.54 vs. 1.32 vs. 1.97%	Smoking time, number of puffs, length of puff, length of hold, interval between puffs, THC plasma concentration, peak subjective high, cardiac acceleration *via* electrocardiogram (ECG).	THC cigarette consumption was dose-dependent when comparing high to low THC content, but there was no evidence of effective titration in THC plasma levels, heart rate acceleration, or reported subjective high.	Yes	No

(Continued)

TABLE 1 | Continued

First author (year published), study location	Study design (sample size)	Sample characteristics	Cannabis products examined	Titration measure	Summary of findings	Evidence of titration behavior	Evidence of effective titration[†]
Herning et al. (14), USA	Experimental, in lab, ($N = 10$)	Experienced in cannabis use, mean age = 29, males	3.9 vs. 1.2% (as cigarette)	Number of puffs, inter-puff interval, puff volume, puff duration, inhalation volume, inhalation duration, cumulative puff volume, cumulative inhalation volume, total smoking duration; physiological measures: heart rate, blood pressure, skin temperature, and expired CO; verbal self-report of subjective high.	The high potency cigarettes were smoked with more puffs and longer inter-puff intervals with greater inhaled volumes of air, thereby diluting the cannabis smoke. Skin temperature and intoxication rating significantly differed between low and high potency conditions.	Yes	No
Chait (15), USA	Experimental, in lab, ($N = 10$)	Experienced in cannabis use, aged 19–33 (mean = 23), 80% males	0.9 vs. 1.7 vs. 2.7% THC (as cigarette)	Amount of cigarettes smoked, cut-off time, expired carbon monoxide levels, heart rate, cigarette questionnaire (taste, harshness, draw), visual analog scales, Addiction Research Center Inventory (ARCI), mood *via* Profile of Mood States (POMS) questionnaire.	The post-smoking increase in expired air carbon monoxide levels and psychological measures did not differ between the conditions.	No	No
Heishman et al. (16), USA	Experimental, in lab, ($N = 12$)	Experienced in cannabis use, aged 23–43 (mean age = 31), males	2.7 vs. 1.3 vs. 0%	Heart rate, smoking topography (inter-puff interval, puff duration, puff volume, maximum flow rate/puff, average flow rate/puff); subjective report of drug effects; a cognitive battery measuring working memory, attention, and motor ability (digit-symbol substation task).	Participants in the high dose condition took smaller puffs, lesser inhalation volumes and shorter puff duration, but did not differ in other smoking topography measures. There was no effect on attention—digit span/symbol substation tasks results did not show a dose-response effect. However, subjective reports of dose-related effects of cannabis were obtained.	Yes	No
Matthias et al. (17), USA	Quasi-experimental, in lab, ($N = 10$)	Experienced in cannabis use, mean age = 23, males	3.95 vs. 1.77 vs. 0%	COHb saturation, self-report subjective level of intoxication, volume and number of puffs and inter-puff intervals, inhaled volume, breath-holding time, respiratory THC retention, heart rate.	Participants in the stronger dose condition showed reduced intake of smoke and tar yield. THC retention and heart rate were increased in the higher THC concentrations.	Yes	No

(Continued)

TABLE 1 | Continued

First author (year published), study location	Study design (sample size)	Sample characteristics	Cannabis products examined	Titration measure	Summary of findings	Evidence of titration behavior	Evidence of effective titration[†]
Hartman et al. (10), USA	Experimental, in lab, (*N* = 19)	Used in past 3 months, at most three times/ week, aged 21–37, 72% males	Placebo (0.008%), low (2.9%), vs. high (6.7%) THC; ground bulk cannabis vaporized *ad-libitum* for 10 min	Blood and plasma cannabinoid analysis.	Of participants that completed all experimental sessions, 10 showed self-titration as indexed by maximum blood THC concentration (μg/L).	–	Mixed
				No behavioral measures of titration presented.	Low concentration cannabis sessions produced consistent max concentration and AUC values in participants, whereas high dose products did not.		
Hartman et al. (9), USA,	Experimental, in lab, (*N* = 19)	Used in past 3 months, at most three times/ week, aged 21–37, 72% males	Placebo (0.008%), low (2.9%), or high (6.7%) THC; ground bulk cannabis vaporized vs. libitum for 10 min	Oral fluid THC concentration.	Max THC concentrations in oral fluid were higher in active (low and high) dose cannabis conditions than placebo. No difference in oral fluid THC were detectable between low and high dose overall or at any timepoint post-dose. Given that differences in blood and plasma were detected in some participants, this suggests a failure of oral fluid THC sensitivity.	–	Mixed
				Blood and plasma cannabinoid (also reported in Hartman et al. (10)).			
Bidwell et al. (11), USA	Experimental (between-subjects), sample recruited *via* social media and mailed flier adverts, (*N* = 121)	Experienced flower or concentrate use, mean age = 28, 55–64% males	Concentrates (70 vs. 90%) or flowers (16 vs. 24%)	Plasma cannabinoids; subjective drug intoxication; mood *via* modified POMS questionnaire; neurobehavioral tasks testing memory, inhibitory control, eyes open, and closed balance.	THC exposure was significantly higher in the concentrates conditions. Neuro-behavioral outcomes did not differ by potency.	–	Mixed
(b) Summary of naturalistic observational studies on titration of recreational cannabis products by potency							
Freeman et al. (4), United Kingdom	Naturalistic observational, recruited by word-of-mouth and snowball sample, (*N* = 247)	Used daily, mean age = 20, 74% males	Own cannabis products varying in potency (1–10) and type (skunk, resin, or herbal); samples analyzed for THC concentrations	Consumption behavior observed from participants smoking their own cannabis in front of the researcher. Self-reported subjective intoxication. Verbal IQ assessed using Wechsler Test of Adult Reading (WTAR).	There was a negative association between THC concentration and amount of cannabis used, but non-daily users were poor in potency estimation.	Yes	Incomplete

(Continued)

TABLE 1 | Continued

First author (year published), study location	Study design (sample size)	Sample characteristics	Cannabis products examined	Titration measure	Summary of findings	Evidence of titration behavior	Evidence of effective titration[†]
					Cannabis product type influenced THC and CBD concentrations. User-estimated potency, in turn, differed as a function of product type, and therefore potency. Amount of product consumed was not influenced by product type/potency. Subjective intoxication did not differ.		
van der Pol et al. (2), Netherlands	Naturalistic observational, "coffee-shops" and chain referral sample, (N=98)	Experienced in cannabis use, aged 19–32 (mean = 24), 75% males	Own products varying in THC concentration, and comparisons of 15.72 vs. 3.64%	Smoking topography measured using a portable device [puff volume, duration, inter-puff interval, average velocity (ml/second), peak flow (ml/second), time to peak puff velocity (ml)].	Higher THC concentration was associated with lower inhalation volume and pace, but not with other topography measures, and positively associated with amount used. The sub-group who used the highest THC product (15.72%) inhaled less than users of average products (3.64%), but the inhalation only halved when the THC concentration was four times higher.	Mixed	Incomplete
(c) Summary of surveyes of cannabis users on titration of recreational cannabis products by potency							
Reinarman (8), USA & Netherlands	Household survey, (San Francisco *N* = 266; Amsterdam *N* = 216)	Experienced in cannabis use, mean age = 34–37, 53–59% males	"Stronger cannabis"	One self-report item: "When using stronger cannabis, do you use…" Less, Same, or More?	Seventy percent of participants self-reported that they use less when using stronger cannabis	Yes	–
Korf et al. (7), Netherlands	"Coffee-shops" field interviews, (*N* = 388)	Smoked cannabis in last 30 days, mean age = 28, 79% males	Own products with dosage assessed using a prompt card showing 0.05, 0.10, 0.20, 0.30 g of cannabis/hash	Self-report of (a) consumption characteristics measured using validated tools, and (b) self-adjustment behaviors in the hypothetical situations that they were smoking more potent products.	Three broad types of cannabis users were identified with mixed results. The type who preferred milder cannabis reported compensating by inhaling less deeply and smoking less. However, the youngest group who consumed the highest monthly dose reported inhaling more deeply, and the oldest group did not report adjustments to intake.	Mixed	–

–, not reported; –, not assessed; AUC, area under the concentration-time curve; CBD, cannabidiol; CO, carbon monoxide; COHb, Carboxyhemoglobin, carbon monoxide that formed when inhaled; THC, tetrahydrocannabinol; POMS, Profile of Mood States.

[†]*Effective titration was defined as adjustments in consumption behavior when using high THC products that resulted in no increase in THC exposure or no differences in neurobehavioral effects.*

In the analyses of blood and plasma THC concentrations (10) 10 of the 19 participants showed evidence of dose titration as indexed by maximum blood THC concentration (μg/L). Specifically, four participants had THC concentrations for the low and high concentration conditions were within 20% of each other, and six participants had greater THC concentrations in the low than the high cannabis condition. Sessions using low concentration cannabis produced consistent THC blood max concentration and AUC values whereas higher dose products did not. This suggests that users attempted to titrate their dose. Data were not presented separately for alcohol and no alcohol conditions, but there were no significant interactions between cannabis dose and alcohol consumption in their effects on THC concentration or AUC.

Bidwell et al. (11) reported a between-subjects experimental study in cannabis users who predominantly used flower/concentrates. They measured blood levels of cannabinoids and the active THC metabolite 11-hydroxyΔ^9-THC (11-OH-THC) and assessed subjective intoxication and mood, and performance on memory, inhibitory control, and balance. Participants were randomly assigned to smoke cannabis products of their preferred type that were standardized to contain either low (flower: 16%; concentrate: 70%) or high (flower 24%, concentrate 90%) THC concentrations.

Blood THC and THC metabolite levels differed between the two forms of cannabis, with concentrates producing higher blood levels than flower (11). There was no significant difference in levels between the two potency levels for cannabis concentrate (70 vs. 90% THC). For cannabis flower, the difference in blood levels approached the pre-specified significance threshold of $p < 0.01$ for blood THC ($p = 0.01$) and 11-OH-THC ($p = 0.02$). Although this effect was not nominally significant, it suggested that participants who predominantly used flower experienced more difficulty adjusting their THC intake.

Concentrate users achieved more than double the mean blood THC level of flower users (11). Despite this difference, self-reported measures of intoxication did not differ between users of the two products. The reason for this discrepancy is unclear. Possible explanations include increased tolerance to THC in concentrate users, a saturation of the cannabinoid receptors so that additional THC intake no longer produced an effect, or differences in user characteristics that affect metabolism/sensitivity to THC. Potency did not significantly affect any of the neurobehavioral measures.

Observational Studies

Observational studies of cannabis users' behavior when using cannabis that varied in potency have shown mixed evidence of titration (2, 4).

Freeman et al. (4) reported an observational study in the UK in which participants used their own cannabis that chemical analyses had established varied in potency and type (skunk, resin, and herbal). Participants were asked to roll a joint and smoke it normally while the researcher recorded their self-reported subjective intoxication and assessed their verbal IQ using the Wechsler Test of Adult Reading.

The study found a negative relationship between THC concentration of the cannabis and the amount of cannabis added to their joints. This relationship was not influenced by the users' frequency of use. The THC levels of the cannabis products were positively correlated with participants' estimation of their potency but the correlation was low. The amount of cannabis consumed was not influenced by product type/potency and participants did not differ in their subjective levels of intoxication.

A similar study in the Netherlands by van der Pol et al. found mixed evidence on whether experienced cannabis users could successfully titrate their THC doses (2). This was a naturalistic, observational study of young experienced cannabis users recruited through "coffee-shops" and chain referrals. The participants used their own cannabis products that varied in THC concentration. Smoking topography was measured using a portable device to assess puff volume, duration, inter-puff interval, average velocity (ml/s), peak flow (ml/s), and time to peak puff velocity (ml).

van der Pol et al. (2) found a positive association between cannabis THC concentration and the amount of cannabis consumed (i.e., participants who used more potent cannabis used larger amounts in their regular joints). There was, however, a negative association between THC concentration of joints and total inhaled smoke volume. This indicated that users inhaled less cannabis smoke when using cannabis with higher THC concentrations. Despite this, they consumed larger amounts when using high potency cannabis. This suggests that their attempt to titrate their doses was only partially successful as measured by THC in blood plasma.

Surveys of Cannabis Users' Behavior

A survey comparing patterns of cannabis use in San Francisco and Amsterdam is often cited as evidence for titration (8). In this study cannabis users were asked: "When using stronger cannabis, do you use less, same, or more?" One-third of respondents reported that they used the same amount, and two-thirds reported that they used less. Those who reported smoking less of "stronger cannabis" said that they preferred to achieve the same effect by using less cannabis. This study can be considered as hypothesis-generating, because it did not employ puff topography or measure THC.

Korf et al. (7) conducted a survey of Netherlands "coffee-shop" patrons who used cannabis and hash products that varied in potency. They collected data on self-reported behavior when smoking more potent cannabis products and identified three groups of users. The first group that varied in age and sex and preferred to use milder cannabis reported inhaling less deeply and smoking smaller amounts of higher potency cannabis. The second was a younger group with more symptoms of cannabis dependence who reported that they inhaled more potent products more deeply. The third comprised older predominantly males with long cannabis careers who lived and smoked alone. They did not report any adjustments in smoking behavior when they used more potent cannabis.

DISCUSSION

This review found mixed evidence on how successful cannabis users were in adjusting their dose of more potent cannabis to achieve the same delivery of THC or the same desired psychoactive effects. Older experimental studies found little evidence for titration but often used cannabis with much lower THC levels that differed minimally between conditions. More recent experimental studies of *ad-libitum* cannabis provided some evidence of titration by finding reductions in the amount of THC in blood and plasma when products of different potency were used. An experimental study of controlled cannabis vaporization found similar THC concentrations in blood in the low and high dose THC conditions in some, but not all, participants. This provides some support that some cannabis users titrate their THC dose during *ad-libitum* consumption (9, 10).

Observational studies found weak evidence that cannabis smokers reduced their THC doses when using cannabis products with higher levels of THC. In surveys, there were self-reported changes in cannabis use but no assessments were made of whether these produced differences in the THC dose consumed or in its physiological or psychological effects.

The question of most relevance to cannabis policy is whether the users of higher THC products do, in fact, titrate their doses. Epidemiological surveys of adverse effects reported by cannabis users suggest that users of more potent cannabis products incompletely adjust their THC doses. In these surveys, consumers of higher THC cannabis products report more negative consequences than users of less potent products (18, 19). A UK cohort study showed that users of high potency cannabis had higher risks of generalized anxiety and cannabis use disorders (20).

There are supportive trends in ecological data. In the USA emergency, hospital, and poisoning center presentations related to cannabis have increased along with the increased use of high THC cannabis products after cannabis legalization (21). In the Netherlands, there was an increase in the number of persons seeking help to quit cannabis as the average THC content of cannabis sold in coffee shops increased and a later fall in numbers when THC content declined (3).

Limitations of the Evidence

This review was severely limited by the dearth of rigorous studies on whether people who use cannabis can effectively titrate their doses of higher potency cannabis. The recent rapid increase in THC potency in cannabis products on the market makes it difficult to compare the findings of early studies that used very low THC cannabis products by comparison with cannabis products now consumed.

There may also have been changes over time in the characteristics of people who use cannabis and in their frequency of use. Tolerance develops with the frequency of cannabis intake so cannabis effects will differ between the occasional users often studied in laboratories and the daily cannabis users who account for most of the cannabis consumed (22).

Routes of administration have also changed over time. Although we did not restrict our search to studies of any specific route of administrations, all the studies we included were of inhaled cannabis products. Methods and ease of titration between different routes of cannabis administration may vary. Vaporization and smoking provide similar cannabinoid delivery (23), but the subjective effects of edible products have a longer time course and users may be at risk of consuming more than intended if they had not waited for them to take effect before deciding to consume more. There are doubts about how well users can titrate their THC doses of oral cannabis products, given that individuals may not know how long they need to wait to assess whether they have reached their desired level of intoxication. Future studies are needed on self-titration of cannabis use by new and emerging administration methods.

Some early laboratory studies of cannabis consumption assessed the relationship between blood concentrations of THC and the effects of cannabis (24). However, many surveys have only assessed titration by self-report rather than measuring the THC content of cannabis or the level of users' intoxication. Self-reported titration can be subject to selective reporting, memory effects and bias and hence provides weak evidence for the titration.

Smoking topography was measured in some studies, with some authors arguing that it is difficult to assess titration without these measures (16). The use of behavioral endpoints as measures is problematic because frequent users have higher tolerance. Objective measures of cannabis potency and THC exposure, such as assessing THC concentration in blood and plasma in laboratory settings, are required in future research on cannabis dose titration.

This review was restricted to papers written in English. The predominance of studies from North America may limit the generalisability of these results. The marketing of high THC content products in the USA may have global impacts as online markets are increasingly popular and merchants accessible through online crypto-markets in the USA are prepared to ship cannabis products worldwide (25).

Our review excluded studies of cannabis when used to alleviate symptoms of chronic medical or mental health conditions. Future research is needed that monitors the prevalence of medical use and assesses the extent to which medicinal cannabis users titrate their doses.

There is an urgent need for larger and better controlled experimental and observational studies of the extent to which cannabis users can and do titrate their THC doses when using more potent cannabis products, such as, cannabis extracts and high potency cannabis flower. This research is needed to inform policymakers on how to reduce harms from the use of high potency cannabis products. It may indicate the need for caps on the potency of cannabis products or higher taxes on more potent cannabis products to discourage their heavy use (26). It is also needed to inform the labeling of THC doses in legal cannabis products that may include standardized THC doses analogous to standard units of alcohol (27).

AUTHOR CONTRIBUTIONS

WH and JL: design and conception. JL, DS, and DD: acquisition and analysis of data. JL and DD: first draft. All authors: interpretation of data, subsequent drafts, revision for important intellectual content, final approval, and agreement to be accountable for the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.630602/full#supplementary-material

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BRIEF RESEARCH REPORT
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Supporting Future Cannabis Policy – Developing a Standard Joint Unit: A Brief Back-Casting Exercise

Hugo López-Pelayo[1], Silvia Matrai[1], Mercè Balcells-Olivero[1], Eugènia Campeny[1], Fleur Braddick[1], Matthijs G. Bossong[2], Olga S. Cruz[3,4], Paolo Deluca[5], Geert Dom[6,7], Daniel Feingold[8], Tom P. Freeman[9], Pablo Guzman[1], Chandni Hindocha[10,11], Brian C. Kelly[12], Nienke Liebregts[13], Valentina Lorenzetti[14], Jakob Manthey[15,16], João Matias[17], Clara Oliveras[1], Maria Teresa Pons[1], Jürgen Rehm[18,19,20,21,22], Moritz Rosenkranz[16], Zoe Swithenbank[23], Luc van Deurse[24], Julian Vicente[17], Mike Vuolo[25], Marcin Wojnar[26,27] and Antoni Gual[1]*

[1] Institut Clínic de Neurociències, Psychiatry and Psychology Service, Grup Recerca Addiccions Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Hospital Clínic de Barcelona, Barcelona, Spain, [2] Department of Psychiatry, University Medical Center Utrecht Brain Center, Utrecht University, Utrecht, Netherlands, [3] Social Sciences Department, Instituto Universitário da Maia (ISMAI), Maia, Portugal, [4] University Interdisciplinary Research Centre for Human Rights - JusGov, University of Minho, Maia, Portugal and JusGov - Escola de Direito, Braga, Portugal, [5] Addictions Department, King's College London, Institute of Psychiatry, Psychology & Neuroscience, London, United Kingdom, [6] Adult Psychiatry Department, Collaborative Antwerp Psychiatric Research Institute, University of Antwerp, Antwerp, Belgium, [7] European Federation of Addiction Societies, Boechout, Belgium, [8] Department of Psychology, Ariel University, Ariel, Israel, [9] Addiction and Mental Health Group, Department of Psychology, University of Bath, Bath, United Kingdom, [10] Clinical Psychopharmacology Unit, Research Department of Clinical and Health Psychology, University College London, London, United Kingdom, [11] National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre, University College Hospital, London, United Kingdom, [12] Departament of Sociology, Purdue University, West Lafayette, IN, United States, [13] Bonger Institute of Criminology, University of Amsterdam, Amsterdam, Netherlands, [14] School of Behavioural and Health Sciences, Faculty of Health Sciences, Australian Catholic University, Fitzroy, VIC, Australia, [15] Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany, [16] Department of Psychiatry and Psychotherapy, Center for Interdisciplinary Addiction Research of Hamburg University (ZIS), University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany, [17] European Monitoring Centre for Drugs and Drug Addiction, Lisbon, Portugal, [18] Institute for Mental Health Policy Research, Centre for Addiction and Mental Health, Toronto, ON, Canada, [19] Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada, [20] Canada Epidemiological Research Unit, Canada Dalla Lana School of Public Health and Department of Psychiatry, University of Toronto (UofT), Toronto, ON, Canada, [21] Technische Universität Dresden, Klinische Psychologie & Psychotherapie, Dresden, Germany, [22] Department of International Health Projects, Institute for Leadership and Health Management, I.M.Sechenov First Moscow State Medical University, Moscow, Russia, [23] Faculty of Health, Public Health Institute, Liverpool John Moores University, Liverpool, United Kingdom, [24] Student Governance and Leadership in European Public Health, Maastricht University, Maastricht, Netherlands, [25] Department of Sociology, The Ohio State University, Columbus, OH, United States, [26] Department of Psychiatry, Medical University of Warsaw, Warsaw, Poland, [27] Department of Psychiatry, University of Michigan, Ann Arbor, MI, United States

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Edited by:
Nicolas Simon,
Aix Marseille Université, France

Reviewed by:
Ruben David Baler,
National Institutes of Health (NIH), United States
SIMONA Pichini,
National Institute of Health (ISS), Italy

***Correspondence:**
Hugo López-Pelayo
hlopez@clinic.cat

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The standardization of cannabis doses is a priority for research, policy-making, clinical and harm-reduction interventions and consumer security. Scientists have called for standard units of dosing for cannabis, similar to those used for alcohol. A Standard Joint Unit (SJU) would facilitate preventive and intervention models in ways similar to the Standard Drink (SD). Learning from the SD experiences allows researchers to tackle emerging barriers to the SJU by applying modern forecasting methods. During a workshop at the Lisbon Addictions Conference 2019, a back-casting foresight method was used to address challenges and achieve consensus in developing an SJU. Thirty-two professionals from 13 countries and 10 disciplines participated. Descriptive analysis of the workshop was carried out by the organizers and shared with the participants in order to suggest amendments. Several characteristics of the SJU were defined: (1)

core values: easy-to use, universal, focused on THC, accurate, and accessible; (2) key challenges: sudden changes in patterns of use, heterogeneity of cannabis compounds as well as in administration routes, variations over time in THC concentrations, and of laws that regulate the legal status of recreational and medical cannabis use); and (3) facilitators: previous experience with standardized measurements, funding opportunities, multi-stakeholder support, high prevalence of cannabis users, and widespread changes in legislation. Participants also identified three initial steps for the implementation of a SJU by 2030: (1) Building a task-force to develop a consensus-based SJU; (2) Expanded available national-level data; (3) Linking SJU consumption to the concept of "risky use," based on evidence of harms.

Keywords: cannabis, standard units, harm-reduction, risky use, prevention

INTRODUCTION

After tobacco and alcohol, cannabis is the most widely used psychoactive substance worldwide. Societies are experiencing a normalization of its use, especially among youth (1) as illustrated by the growing phenomena of coffeeshops and cannabis social clubs (2). Cannabis policy is shifting worldwide as the supply is moving from an unregulated (illicit) market to an open market for an "ordinary commodity" (e.g., in Canada, Uruguay and several states within the US). Observing that public opinion on the legal status of cannabis in Europe is also changing, European countries likely will not be an exception to this trend over the coming years. This changing context (i.e., in social perceptions and in legal context in some countries) aligns cannabis use in high-income countries more closely with alcohol or tobacco than to currently illegal drugs. A transition to legal, regulated access will require new prevention and harm-reduction strategies to minimize adverse effects as cannabis becomes more widely available (3). However, evidence also points to higher THC concentration in cannabis products during the last decade, which is believed to be associated with an increased risk of acute, and chronic health problems, especially in adolescents (4). Additionally, the National Institute on Drug Abuse has already expressed plans to "explore the possibility of constructing a standardized dose similar to that for alcohol (the standard drink) and tobacco (a cigarette) [. . . for cannabis] for researchers to employ in analyzing use and [. . .] for users to understand their consumption (5)." Learning from the history of measuring standard units, i.e., alcohol and tobacco, could facilitate public health, research and clinical professionals to navigate this new context more successfully and prevent errors from being repeated. During the 1980s and 1990s, several countries reached a national consensus defining their Standard Drink (SD) (6). Researchers conducted field tests in several countries to grow comparative evidence and adapt prevention efforts to the cultural characteristics of the country (7). However, most countries did not re-validate the SD with the field test (8). As a result, there are large differences between countries in defining SD, due to the fact that some are based on national consensus while others derive from experimental research, making useful cross-country comparison, policy analysis and prevention efforts more difficult. Nonetheless, despite its limited accuracy, the SD has advanced the alcohol public health field considerably: the SD provides clinicians, public health specialists, policy makers, and researchers with a common tool for assessing alcohol use and implementing programs from early identification of risky use (9) to monitoring consumption in harm-reduction (10).

Other relevant instruments for assessing alcohol use were based on the SD [AUDIT (11), ISCA (12), AUDIT-C (13), HRAR (14)] and are widely implemented globally. Screening and Brief Interventions (SBI) programs, make use of these instruments, are cost-effective in 24 out of 28 EU countries and cost-saving in 50% of countries (15). Learning from practical experiences in the alcohol field and the development and use of SD, the following should be essential characteristics in developing a Standard Joint Unit (SJU): (1) a high degree of evidence-based consensus on equivalence between countries; (2) high accuracy (providing a faithful representation of real doses); (3) taking into account less common routes of administration (cannabis is consumed in more varied ways than alcohol or tobacco); (4) built in monitoring of changes in patterns of use and chemical composition. Having said this, many peculiarities of cannabis use present challenges in the development of standard units for cannabis, among these are: different routes of administration (smoking, vaping, edible), concurrent use with other substances (e.g., tobacco, alcohol), heterogeneity of quantities or interactions among different cannabinoids (THC/CBD) (16). Standard units for cannabis, based on a fixed dose of THC, have the potential to address some of these challenges (16). What constitutes a SJU is important to consider. Currently, studies have gathered evidence on typical joints in Australia (140 mg cannabis/joint), Spain (250 mg of hashish or cannabis plant/joint and translating into 7 mg THC/joint), The Netherlands (260 mg cannabis/joint), UK (140 mg cannabis/joint and 380 mg cannabis/joint), USA (660 mg cannabis/joint vs. 580 mg cannabis/joint vs. 700 mg cannabis/joint) (17–24). Only the Spanish study reported milligrams of THC in a typical joint. Although a commendable start, these studies were heterogeneous regarding both methods (real/simulated cannabis, ecological/lab studies, etc. . .) and results, even within countries. In the European Web Survey on Drugs (25), the EMCDDA also asks about usual amount consumed for herbal cannabis and cannabis

resin. The rapid growth of research in this field also means that reaching a consensus on SJU research methodologies to support clinical implementation is an urgent issue. In order to advance this area, we organized a workshop, as part of the Lisbon Addictions Conference 2019, with experts in different disciplines (sociology, psychology, public health, basic and clinical research, psychiatry) and with the following objectives: (1) to reflect on the challenges to reaching a consensus on an operative SJU; (2) to reflect on opportunities and facilitators to achieving an SJU; (3) to propose different trajectories to achieve the main goal: implementation of a European SJU by the year 2030; and (4) to reach a minimum-level consensus on the first step toward achieving a SJU. The expected outputs were: (1) consensus on the first-steps toward achieving an SJU; and (2) a preliminary annual roadmap to develop a SJU by the year 2030.

METHODS

The Back-Casting Exercise (BCE)

An operational definition of a BCE is "a scenario technique where normative targets or unwanted outcomes are defined by a group for the purpose of formulating ways in which such goals can be achieved or avoided" (26). Participants in back-casting exercises do not predict the future, but rather choose the desirable future and work backwards to define the steps to achieve that goal (26). Back-casting is a prospective method in the context of foresight methodologies. Foresight methodologies are "frameworks for making sense of data generated by structured processes to think about the future" (27). A back-casting exercise is useful when (28, 29):

1. the problem is complex, persistent, and predominant.
2. change is very necessary.
3. sustainability of the solution is relevant.
4. long-term planning (at least 5 years) is needed.
5. the results of the exercise could impact multiple stakeholders and could empower the participants in the exercise.

The organizers pre-defined the desirable future in 2030 based on their professional expertise in the alcohol and cannabis areas (see **Figure 1**). The contrast between desirable future and current scenario (see below) is the starting point for the workshop discussions. The current scenario was defined as:

- The populations at risk of suffering cannabis-related health problems are not well-identified.
- The assessment of cannabis use patterns is usually based on frequency of use (e.g., days) only.
- A clear public health message about "how much is too much" does not exist because low-risk use is not well-defined.
- The prevalence of risky use (in different populations) is unknown due to lack of risk level definitions.
- Evidence-based practices to reduce cannabis-attributable harms (i.e., SBIRT) are not implemented.

Participants

A total of thirty-two experts attended the workshop. Participants were scholars and practitioners from a range of disciplines: basic research ($n = 1$), pharmacology ($n = 1$), neuroimaging ($n = 3$), social sciences ($n = 3$), psychology ($n = 3$) and other clinical research ($n = 10$), public health ($n = 4$), epidemiology ($n = 4$), law and criminology ($n = 2$). Furthermore, one cannabis industry representative participated. Experts were divided into five transdisciplinary groups. Participants came from several different countries (in descending order of number): UK ($n = 7$), Spain ($n = 5$), Portugal ($n = 5$), The Netherlands ($n = 3$), USA ($n = 2$), Germany ($n = 2$), Australia ($n = 2$), Belgium ($n = 1$), Hungary ($n = 1$), Poland ($n = 1$), Cyprus ($n = 1$), Israel ($n = 1$) and Canada ($n = 1$). Participants had either pre-registered for the back-casting workshop ($n = 21$) or arrived to participate spontaneously ($n = 11$) (these participants were admitted until all available seats were occupied). The workshop was comprised of both academics invited, based on their expertise ($n = 17$); and participants from the conference ($n = 15$) (see **Figure 2**).

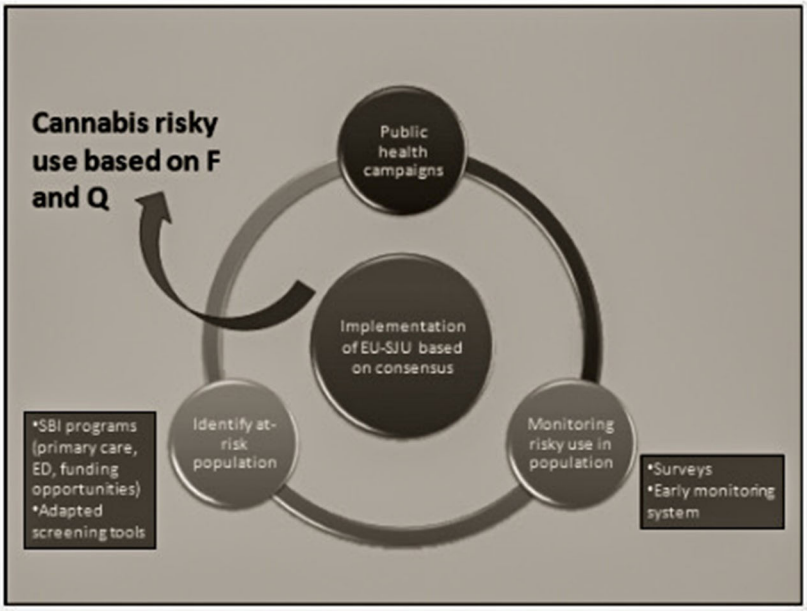
In order to facilitate the workshop dynamics and facilitate a smoother running of the exercise, those who had previously registered received a 3-page background document on the SJU concept, the back-casting method, and relevant key references, along with the following advice: (1) An absolute consensus is not expected. Please focus on achieving minimum consensus; (2) Try to find cause-effect relationships; (3) Try to focus on one future desirable scenario; and (4) Do not attempt to predict the future but rather consider the desirable future. The exercise was led by two clinician scientists, both with extensive experience in participatory workshops (AG and HLP). Three researchers – two of them with ample experience in participatory processes – collaborated in the design, preparation, and deployment of the workshop, and the analyses of the results (SM, EC and FB). These five experts conceptualized, designed and developed the exercise.

Procedure (90 min)

We prepared and set up the back-casting exercise in the following steps (adapted from "STD back-back casting approach" and Wilson et al. 2006) (30):

Step 1 (10 min): Introduction - The first part of the session was dedicated to explain the rationale underlying the workshop, its objectives, methodology and expected outcomes. Afterwards, a description of the current scenario and a future desirable scenario was presented to the participants, with sufficient time reserved for questions or amendments to both current and future scenarios.

Step 2 (20 min): Prioritizing relevant elements - Activity 1 was explained and participants were allocated to small multi-disciplinary groups (6–7 people) for the first part. They had three lists of elements referring to the SJU: (i) challenges, (ii) facilitators, (iii) values (see **Supplementary Tables 1**–**3**). The lists included a definition for each concept. Participants could propose new items if they considered that the definition was not accurate or if a concept was missing. Each small group was instructed to choose by consensus the five most relevant concepts from each list. In the second part of the exercise the whole workshop group worked together and voted on each concept for relevance, after hearing the outcomes of previous consensus discussions.



Consensus about SJU exists and allows cultural and contextual adaptations	An early monitoring system allows the definition of SJU to be readapted when the generalized pattern of use changes.
Populations at risk of suffering cannabis-related harms are well identified	Risky cannabis use is well-defined, in terms of the number of standard joints per occasion and frequency of use (i.e. quantity and frequency occasions (QxF), individual and contextual factors.
Screening tools for risky use have been adapted and validated to detect threshold levels of the SJU and frequency of use (QxF) occasions.	European population surveys also include QxF questions allowing assessing the prevalence of risky cannabis use.
There are public health campaigns to communicate levels of high risk use, and initiatives to monitor the impact of the health campaigns. Primary health care professionals routinely ask patients about their cannabis use.	Evidence-based prevention and intervention, for instance SBI programs for risky cannabis users are funded by national health systems. There are research funding opportunities to address the implementation of evidence-based prevention and intervention programs for risky cannabis use, beyond those given in primary care.

SBI= Screening and Brief Interventions; ED=Emergency Departments; SJU=Standard Joint Unit; QxF or F and Q= Quantity and Frequency

FIGURE 1 | Hypothetical desirable future in 2030, used to guide the back-casting workshop.

Step 3 (30 min): Back-cast trajectories - Activity 2 from future to present was performed by each small group ($n = 5$, of 6–7 participants each). The groups focused on a specific key element of the bigger desirable future scenario, and each had a card with the description of this element (group 1: Primary care; group 2: Prevention; group 3: Cannabis users; group 4: Epidemiology; group 5: Research). Using a pre-designed canvas, each group deconstructed the route toward the end-point of the specific scenario element in 2030, starting in 2020 (see **Supplementary Table 4**). At the end of this exercise, the results were briefly shared with the other members of the workshop.

Step 4 (10 min): Defining key events - this slot was allocated to a discussion across the groups of cornerstones, milestones, and first steps based on the reflection during the exercise and the professional background of the participants.

Summary (5 min): The exercise ended with a brief summary given by one of the participants (TPF), as rapporteur of the group. The participant was one of the coordinators of the preconference workshop "International Cannabis Toolkit," in order to link these events. (https://www.lisbonaddictions.eu/lisbon-addictions-2019/side-events). The context of the FuturiZe Project and the Lisbon Addictions Conference is explained in the **Supplementary Material**.

Analyses

Descriptive analysis of the workshop was carried out by the organizers and shared with the participants in order to

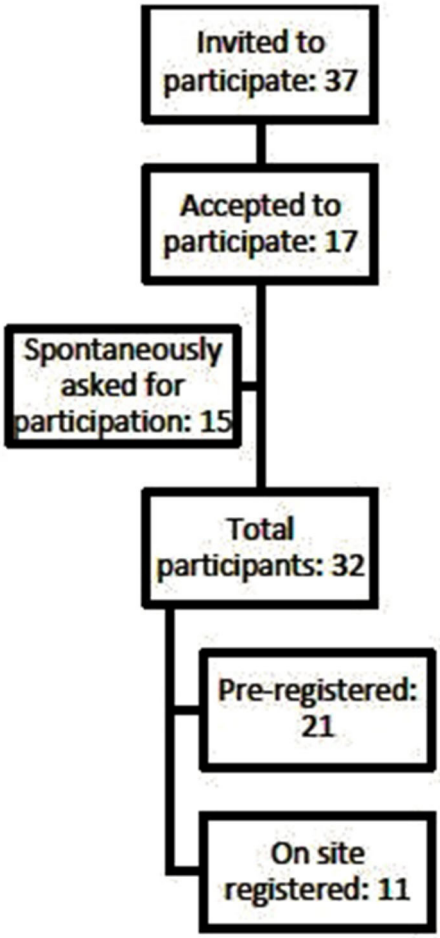


FIGURE 2 | Recruitment process of participants in the workshop.

suggest amendments. No quantitative or qualitative analyses were conducted.

Ethical issues: Under Spanish law, no ethical approval was required for this study in which the data is expert opinion.

RESULTS

Future Desirable Scenario

The workshop participants did not raise any modifying comments or objections on the desirable future scenario (i.e., implementation of a SJU based on consensus) as proposed by the organizers, and approved unanimously it (see **Figure 1**).

Defining Values, Challenges and Facilitators (Supplementary Tables 1–3 Respectively)

The five most highly voted defining values associated with SJU were "easy-to-use" (straightforward, clear instructions and simple to use correctly, 100%), "universal" (appropriate for or adjustable to all settings/contexts, 100%), "accounts for THC" (quantity of use register will only include THC, 80%), "accurate" (providing a faithful representation of someone or something, 60%) and "accessible" (easily understood or appreciated, 60%). The five most highly voted challenges were: "sudden changes in patterns of use" (quick and unexpected changes in the behavior of cannabis users which impact the validity/accuracy of the SJU, 100%), "heterogeneity of cannabis compounds" (diversity in content/composition, 80%), "heterogeneity of THC concentration" (diversity on THC content for the same grams of herbal or resin, 80%), "heterogeneity in routes of administration" (diversity in routes of administration (smoking, vaping, edible, etc.), 60%) and "laws" (legal status of marijuana (e.g., possession being criminal offense) in many countries, 60%). "Synthetic cannabinoids" were proposed as a separate additional challenge by one participant, but this challenge was included by consensus of participants in the category of "heterogeneity of cannabis compounds." The six most highly voted facilitators were: "previous experience in other standard measurements" (Learning about the limitations and strengths of standardization of typical dose and operational definitions of risky use in tobacco or alcohol, 100%)," funding opportunities available" (money provided, especially by an organization or government, for drug research is now addressed to the area of cannabis, 80%), "cannabis users' support" (organized or non-organized users whose messages are partially or totally in line with the objectives of the SJU 80%), "policy-makers' support" (roadmap or agenda of policy-makers is partially or totally in line with the objectives of SJU, 60%), "high prevalence of use" (health topic becomes more prevalent and more mainstream,60%), "depenalization, decriminalization and legalization in many countries" (changes in laws regarding cannabis which facilitate research into cannabis and the implementation of solutions conducive to harm-reduction approaches, 60%). "New advances in laboratory studies" were proposed and accepted as an additional facilitator, which was voted on by a majority of the groups (60%).

Back-Casting Trajectories (From 2030 to 2020) and Milestones (Supplementary Table 4)

The most salient milestones reported by participants were: (1) negotiate and engage the stakeholders as an ongoing process; (2) set of scenarios (options) to discuss the analytical phase; (3) guidelines for using the SJU (setting, protocols, etc.); (4) definition and consensus of SJU [and conversion to standard cannabis unit (16)]; (5) programs funding EU-wide research in the cannabis field; (6) external validation (statistical concept) of SJU (e.g., indicators) before clinical programs; and (7) data collection (dose per joint) at the country level. Consideration of whether it is inappropriate (e.g., normalization of drug-using behavior and reduced perception of risk) or appropriate (e.g., reducing stigma and increasing help-seeking) to use the term "standard" when it comes to a substance that is illegal in many jurisdictions also arose as relevant point during the workshop process.

First Steps

The first three steps (to be implemented concurrently) were: (1) Set up a "Task Force" that could also act as a lobby for the European Commission and influence the European Union (EU) Research Agenda, raising the profile of this subject; (2) Conduct a review of already available data at the national level; (3) Emphasize the need for SJU in terms of risks.

DISCUSSION

The 21st century has been characterized as an "Information Age," where technologies facilitate the use of information by citizens. The SJU provides an opportunity to capitalize on this desire for information by working toward a clear evidence-based standard which consumers can rely upon. In addition to leveraging consumer desires for information, the SJU provides important opportunities for harm reduction and intervention as the use of cannabis continues to expand in the future. In fact, although our proposal of establishing a SJU is mainly focused on regulation of recreational use, it might also be useful to achieve a better control of those preparations intended for a potential medical use, which are also generating growing interest in the last years (31). Given the importance of these standards for the future of cannabis consumption, the process of identifying the most efficient and accurate means to develop the SJU remains a critical task. The results described above used established expertise across multiple scientific domains to identify how these standards may be achieved. According to the expert opinion from the workshop group, the SJU must be easy-to-use, universal, take into account only the concentration of THC, and be accurate, and accessible ("easily understood or appreciated"). With the aim of overcoming the barriers identified and enhancing the effect of the facilitators, the experts suggested one main step to be implemented: creating a task force to emphasize the need for the development of an SJU. This task force should generate input for the EU Research Agenda and promote a review of the available data at the national level. The majority of defining values reported by the participants were also presented in two recent opinion papers (e.g., assessing only THC, accessible, universal and easy-to-use) (16, 32). The SJU should be accurate (defined as "providing a faithful representation of something") according to attendees, being different to the SD, which prioritized utility over accuracy (6). Most of the challenges discussed [i.e., heterogeneity of routes of administration, laws, variations over time in THC concentrations (33), compounds and patterns of use] have also been repeatedly reported as limitations in previous research (16, 17). Future research must cope with these barriers by incorporating new methods [e.g., trend-spotter method (34), foresight methods (27), participatory research (35), etc.]. An SJU Task Force should share the necessary knowledge, skills and expertise in such new methods. The current legal status of cannabis in 12 European countries is more flexible now than it was a few years ago (e.g., incarceration is now not possible for minor cannabis possession in these 12 countries) and continues to change (e.g., the government of Luxembourg is set to provide legal access to cannabis in the near future). These evolutions in policy could easily open up more research opportunities in this area (36, 37). Cannabis is high both on the research and regulatory agenda – a PubMed search using the terms "marijuana OR marihuana OR cannabis" showed 388 papers in 1998 and 2,190 papers in 2018, thus research interest, measured by published papers, has increased by 460% within two decades. Over the same period, the increase of the number of papers studying "cocaine" was only 8.2%. These patterns reflect a growing interest in this research area, an interest that might act as a facilitator for establishing a SJU research agenda, making it important for researchers to use this momentum to promote the specific line of research on the SJU. Increased funding opportunities in Australia, North America, and Europe are beginning to facilitate much needed research to establish the SJU. The National Focal Point in Spain for the EMCDDA (Plan Nacional sobre Drogas) funded two projects related to the SJU. NIDA also funded research for screening and brief assessment, development and impact assessment of prevention programs on marijuana use and patterns and trends in marijuana use and attitudes (38). These topics are closely related to the development of an SJU. In 2015, NIDA invested US$ 66M in cannabis research [> 10% of all research project grants, US$ 625M (39)]. In Europe several opportunities exist, for example: Supporting Initiatives in the Field of Drugs Policy (JUST-DRUGS-AG HOME Action Grant) and European Cooperation in Science and Technology (40, 41). Recently, NIDA launched a request for information inviting Comments on the Establishment and Implementation of a Standard Unit Dose of Δ-9-tetrahydrocannabinol (THC) for Cannabis Research (42). Moreover, the fact that cannabis is the most widely used psychoactive substance beyond alcohol and tobacco, with some authors even claiming that there is a certain normalization of its use, should also stimulate research in order to overcome the gaps in the specialized literature. Taking advantage of funding opportunities was critical, according the expert opinion of participants, in order to enable the creation of a task force that allows oversight of the available data at the national levels, and to act as lobbying force to influence a cannabis research agenda. This network could both facilitate research and be involved in training relevant workforces in use of the standard measures.

Limitations and Strengths

The main limitation to our workshop back-casting exercise was a time constraint (90 minutes vs. 4 or more hours for other published BCEs), which may have resulted in less intermediate analyses between description and consensus of desirable futures (step 1), and back-cast trajectories (step 2) (43). However, this brief and concentrated version of BCE allows for the inclusion of a large number of diverse experts who otherwise would not have been able to attend for timetabling or financial reasons. Another secondary limitation is the limited heterogeneity of participants (with few from outside academia). Fortunately, we think that synergies with other activities in the LxAddiction2019 Conference will have mitigated these limitations (e.g., a preconference Workshop on 'International Cannabis Toolkit' https://canntoolkit.com/ and a "Big Debate" session on Day 1 of the conference programme: 'Will changes

in cannabis policy result in greater costs or greater benefits?'). The strengths of this BCE exercise were the relevant expertise in this specific research area of the vast majority of participants; heterogeneity of research profiles involved (basic science, social science, epidemiology, neuroimaging, pharmacology, clinical research) and the inspiring context of the FuturiZe Project and conference which facilitated creativity and the opportunity for participants to engage in a co-creative exercise.

CONCLUSIONS

The implementation of a SJU in 2030 was considered feasible after overcoming several barriers and harnessing contextual facilitators. Experts agreed that an SJU is possible on the basis on the following achievements: (1) the building of a task force to define, develop and advocate for an evidence-based SJU; (2) reviewing and expanding available national-level data on cannabis use and related risks; and (3) examining how the SJU relates to the concept of "risky use" of cannabis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HL-P, AG, SM, EC and FB designed the workshop and the study (conceptualization), and conducted the analyses. HL-P wrote the first draft (writing original draft). All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.675033/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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The Relationship Between Childhood Physical and Sexual Abuse and Adolescent Cannabis Use: A Systematic Review

Víctor De la Peña-Arteaga[1,2]*, *Sarah O. Nogueira*[1,2], *Michael Lynskey*[3] and *Lindsey A. Hines*[4]*

[1] Bellvitge Biomedical Research Institute, Barcelona, Spain, [2] Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain, [3] Addictions Department, Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London, London, United Kingdom, [4] Centre for Academic Mental Health, Population Health Sciences, University of Bristol, Bristol, United Kingdom

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Daniel Feingold,
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***Correspondence:**
Víctor De la Peña-Arteaga
vdelapena@idibell.cat
Lindsey A. Hines
Lindsey.hines@bristol.ac.uk

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Background: Among adolescents, cannabis use is a health concern due to associations with drug addiction and mental health disorders across the life course. It has been shown that childhood maltreatment is associated with drug addiction in adulthood. However, a better understanding of the relationship between maltreatment and drug use may improve targeted prevention and interventions. The aim of this systematic review is to describe the association between exposure to childhood maltreatment, specifically physical and sexual abuse, with adolescent cannabis use.

Methods: A systematic search strategy was applied to Embase, PsycINFO, and Ovid MEDLINE(R) databases. Methods followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Abstract and title screening was performed to identify papers which reported an estimate of the association between childhood physical or sexual abuse and adolescent cannabis use. Full text screening of each paper was performed, and data were extracted and study quality assessed. Weighted means meta-analysis was performed on studies reporting odds ratios as effect estimates.

Results: Of 8,780 screened articles, 13 were identified for inclusion. Eight papers received a quality rating score indicating lower risk of bias. Eleven papers reported the relationship between childhood sexual abuse and adolescent cannabis use; effect estimates ranged from AOR 0.53–AOR 2.18 (weighted mean OR 1.29, 95% CI 1.08–1.49). The relationship between childhood physical abuse and adolescent cannabis use was reported in 7 papers; effect estimates ranged from AOR 1.25–AOR 1.87 (weighted mean OR 1.39, 95% CI 1.12–1.66). Differences in the strength of the evidence were observed by the method of exposure ascertainment, and there was some evidence of differences in association by gender, age of cannabis initiation, and the severity of the abuse.

Conclusions: This systematic review indicates childhood physical or sexual abuse may increase risk of adolescent-onset cannabis use. Few studies considered variation in timing of onset, or by gender. Adolescent cannabis use precedes is strongly associated with increased risk of negative mental health outcomes; further exploration of adolescent cannabis use's place on the causal pathway between childhood abuse and adult mental health problems is warranted to improve intervention.

Keywords: childhood maltreatment, physical abuse, sexual abuse, adolescence, cannabis, drug use, systematic review

INTRODUCTION

Globally, cannabis is the most commonly used internationally regulated drug (1). Adolescence is a key period for initiation of cannabis use (2). Cannabis use in adolescence is considered an area of public health concern as adolescence is recognised as a key period for development (3, 4) and there is research associating drug abuse with neurobiological changes in the developing brain of adolescents (5). There are notable recent changes regarding cannabis; policy on its use is becoming more liberal worldwide (6), and cannabis use is increasing amongst young Europeans, with prevalence of past-month use amongst those aged 15–34 years estimated at 5.4% in 2017 (7).

Adolescent cannabis use is a key target for early intervention strategies (8). Recent reviews have identified that adolescent cannabis use raises likelihood of depression and suicide attempts in later life (9), and cannabis use is consistently associated with increased likelihood of psychosis (10). Additionally, adolescent cannabis use is associated with poorer education and employment outcomes (11–13), and with acute risks from use such as car accidents (14). In a stage-sequential model of drug use and addiction, initiation of drug use is a necessary stage before individuals can escalate in frequency of use and problematic use (15). Exploring the early stages of drug use can have implications for better understanding of the pathways that lead to adult addiction and mental health disorders. Consequently, there is value in identifying risk factors for adolescent cannabis use in order to target prevention and intervention efforts.

A known risk factor for addiction is childhood adversity. Meta-analyses have shown that experiencing Adverse Childhood Experiences (ACEs) can raise the likelihood of experiencing negative physical and mental health outcomes (16, 17). Recent systematic reviews and meta-analysis (18–20) have found evidence for an association between childhood maltreatment or past traumatic events and drug problems later in life. However, these reviews have focussed mainly on dependence across the life course. The authors are unaware of a review which has focussed exclusively on non-problematic cannabis use during adolescence.

Previous reviews have focussed on broad conceptualisations of childhood adversity and trauma, but it is not clear that all childhood ACEs (classically conceptualised as sexual, physical or emotional abuse, emotional neglect, substance abuse by the parents, parental mental illness or suicide attempt, violence between parents, parental separation, bullying and parental criminal conviction) have the same relationship to outcomes. In the present review, we explore childhood physical abuse (CPA) and childhood sexual abuse (CSA) as risk factors. It is estimated that, globally, half of all children will experience or witness some form of violence in childhood (21). Although global meta-analyses estimate the prevalence of physical and sexual abuse to be minimal to moderate severity (22), childhood physical and sexual abuse in childhood are both public health concerns given their association with negative outcomes across the life course (23). In relation to cannabis use and dependence, a study breaking down risk factors by stages of drug use found a relationship between CSA and exposure to cannabis, but not progression to dependence (24). Studies of these risk factors for illicit drug use have contradictory findings, with physical abuse more strongly associated than sexual abuse in some studies (25, 26), while others show the opposite relationship (27).

This systematic review focusses on general population studies to describe the association between exposure to the adverse childhood experiences of physical and sexual abuse and adolescent cannabis use. We explore the quality of the literature on the relationship between childhood physical and sexual abuse and discuss the consistency of findings and the implications for cannabis use.

METHODS

Research Design

The present study consists of a systematic review of the literature based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Information Sources

The electronic databases used for this systematic review were Embase, PsycINFO and Ovid MEDLINE(R). The search was performed at two different points in time: June 2017 and September 2020.

Search

The following search terms were used to perform the search in the electronic databases [selected using a Participants, Interventions, Comparators, Outcomes, and Study design approach (28)]:

[(Teenage or Adolescent or Adolescence or Youth or Child) and (Maltreatment or "Child abuse" or "Sexual abuse" or "Physical abuse" or "Adverse experience" or Trauma or Stress) and ("Misuse" or "First use" or Initiation or "Illicit use" or "Use" or "Abuse" or Experimentation) and (Drug or "Illicit drug" or

Cannabis or Marijuana or Hash* or Skunk or Opiate or Heroin or Stimulant or Alcohol or Chemsex or "Novel Psychoactive Substance" or "Legal high" or Ecstasy or Cocaine or Meth or Tobacco or Nicotine or Cigarette)].tw.

The search was limited by title and abstract content (.tw.). No further limits were used. Alcohol, tobacco and other illegal drugs search terms were included to ensure capture of papers where cannabis use was a secondary focus.

Eligibility Criteria

Inclusion/Exclusion Criteria

Studies were included if they met the following inclusion criteria:

1. Reported as part of a peer reviewed journal and as part of the databases used to the search or their references.
2. Individuals were up to 26 years old. This age range encompasses contemporary patterns of adolescent growth and their social role transitions (29), as well as capturing a period in which neuronal connexions are continuing to develop (30).
3. Papers published in English.
4. General population samples.
5. Included a measure of association between childhood physical or sexual abuse and cannabis use.

Studies were excluded if:

1. Reviews, meta-analysis, conference abstracts, dissertations, lectures, book chapters or incomplete articles.
2. Regarding sample: excluding
   a. Individuals diagnosed with addiction or substance use disorder.
   b. Animal studies, due to the aim of researching human adolescence.
   c. Groups of drug using participants only or inpatients of an addiction clinic.

Study Selection

Once the search was run, by two researchers (VDA and SON), results were exported into a reference manager software. Duplicates were removed using the same software and afterwards an abstract and title screening was performed to obtain the relevant full text studies. During this stage, papers were excluded using the criteria stated above.

Subsequently full text screening was performed by researcher review (VDA and SON) of each paper. Inclusion and exclusion criteria were applied as above to determine suitability for inclusion in review. Papers excluded at this stage mainly represented the ones outside of the age range or focused exclusively on cannabis use disorders rather than cannabis use.

As mentioned, the full search and screenings were performed by two researchers independently. Afterwards, each inconsistency was examined by another researcher (LH) to obtain a final list of included papers. To finalise, references of key papers were manually screened to ensure review completeness.

Quality Assessment

An adapted version of the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses [by Wells et al. (31)] was used for this review. With this tool, each study was judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. Once again, papers were rated for quality by two researchers independently (VDA and SON) and inconsistencies were reviewed by a third researcher (LH).

Weighted Mean Meta-Analysis

The studies reporting Odds Ratios (OR) and Confidence Intervals (CI) were entered into a weighted mean meta-analysis. Weights were assigned to each study taking into account each sample size and OR. This was obtained to summarise the global magnitude of effect sizes with the available data.

RESULTS

Study Selection

The final study selection of 13 papers is fully shown in **Figure 1**. Characteristics of each of the included studies can be seen in both quality assessment table (**Table 1**) and data extraction table (**Table 2**) (32–44).

Quality Assessment and Risk of Bias

According to the quality rating scale, one paper achieved the maximum rating of eight (42), and three got a very high grade of seven (38–40). A further eight papers received five or more of the available quality rating points and only one paper obtained a very low score of two (43).

Studies did not consistently differ by the representativeness of the cohort or the selection method of participants. Contrastingly, other rated categories, as control for confounders, ascertainment of childhood abuse, or data collection's start point were very different among studies. These differences created most of the variations seen in the final ratings. The interrater reliability between researchers was 0.42 (Kappa value).

Definition of Physical and Sexual Abuse

Nine out of 13 papers used non-structured and structured self-reported scales (**Table 2**). Only one of these papers (39) included interviews as part of the assessment. The remaining four papers (33, 40, 41, 44) used data from child protective services records.

Three studies (34, 35, 44) differentiated outcomes based on the number or type of traumatic events. One study (34) made a differentiation between being sexually abused once or twice, three or more times and raped. When comparing frequency of events in adjusted models; occasional cannabis use Adjusted Odds Ratios (AOR) was 1.4 (95% CI 1.0–2.0) when sexual abuse was once or twice, compared to an AOR of 2.1 (95% CI 1.4–3.3) when sexual abuse was experienced three or more times. In contrast, frequent cannabis use AOR was 2.8 (95% CI 1.7–4.4) when sexual abuse was once or twice compared to an AOR of

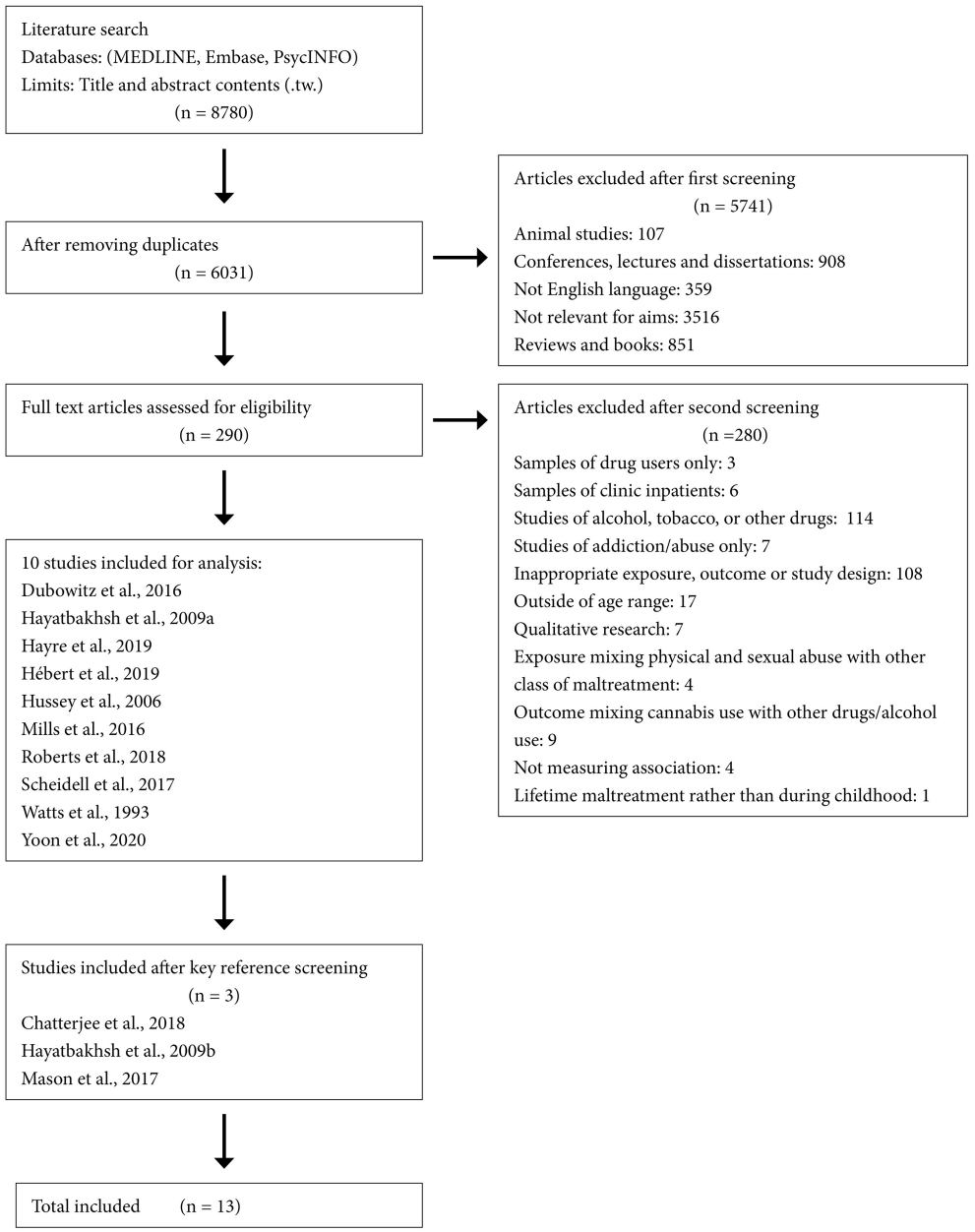

FIGURE 1 | Flowchart of search results.

3.6 (95% CI 2.0–6.4) when sexual abuse was experienced three or more times.

Additionally, one study (35) explored differences between the type of sexual abuse, comparing non-penetrative or penetrative. It did not identify differences for type of sexual abuse (35), finding an effect of AOR 1.7 (95% CI 1.3–2.2) for non-penetrative sexual abuse on any cannabis use, compared to AOR 1.8 (95% CI 1.3–2.7) for penetrative sexual abuse on any cannabis use.

One study (44) differentiated between timing of abuse for the association with cannabis use. Odds of recent cannabis use aged 12–18 were increased amongst those reporting adolescent physical abuse (AOR 1.87, 95% CI 1.06–3.32), but were not significantly different among those reporting early childhood physical abuse (AOR 1.72, 95% CI 0.95–3.10), early childhood sexual abuse (AOR 0.55, 95% CI 0.25–1.21) and middle childhood sexual abuse (AOR 0.53, 95% CI 0.22–1.26).

Association Between Childhood Maltreatment and Adolescent Cannabis Use

For sexual abuse, a significant association between the exposure and adolescent cannabis use was observed in 5 of the 11 studies which focussed on this form of abuse (34, 35, 38, 39, 43), and

TABLE 1 | Quality rating.

References	Representativeness of the cohort	Selection of participants who did not experience childhood abuse	Ascertainment of childhood abuse	Did data collection start before participants started using cannabis?	Did the study control for confounders that will make samples comparable?	Was follow-up long enough for outcomes to occur	Adequacy of sample retention	Total
Chatterjee et al. (32)	1	1	0	0	2	0	0	4
Dubowitz et al. (33)	1	1	1	1	0	0	1	5
Hayatbakhsh et al. (34)	1	1	0	1	2	0	1	6
Hayatbakhsh et al. (35)	1	1	0	1	1	0	0	4
Hayre et al. (36)	1	1	0	0	1	0	1	4
Hébert et al. (37)	1	1	0	0	1	0	1	4
Hussey et al. (38)	1	1	1	1	2	0	1	7
Mason et al. (39)	1	1	1	1	1	1	1	7
Mills et al. (40)	1	1	1	1	2	0	1	7
Roberts et al. (41)	1	0	1	1	1	1	1	6
Scheidell et al. (42)	1	1	1	1	2	1	1	8
Watts et al. (43)	1	1	0	0	0	0	0	2
Yoon et al. (44)	1	1	1	1	0	0	1	5

Selection
Representativeness of the cohort.
Max 4*
**truly/somewhat representative cohort sample; 0 selected group e.g., volunteers/no sampling description.*

Selection of the participants who did not experience childhood abuse.
**from the same community as the exposed cohort; 0 different source/no description.*

Ascertainment of childhood abuse.
**secure record (government record)/structured interview; 0 written self-report/no description.*

Did data collection start before participants started using cannabis?
**yes; 0 no.*

Comparability
Max 2*
Did the study control for confounders that will make samples comparable?
**study controls for sex/gender; * study controls for SES.*

Outcome
Max 3*
Was follow-up long enough for outcomes to occur.
**yes - followed up past age 25; 0 no.*
**complete follow up - all subjects accounted for.*

Adequacy of sample retention.
**subjects lost to follow up unlikely to introduce bias – > 60 % follow up, or description provided of those lost;*
0 follow up rate <60% and no description of those lost/no description of retention or sample loss.

Total maximum: 8*

5 of the 11 studies reported weaker, non-significant evidence (33, 40–42, 44). One study (37) stratified by gender and found a significant association in females (OR 2.18, 95% CI 1.84–2.59), but a non-significant association for males (OR 1.28, 95% CI 0.88–1.84). Adjusted odds ratios ranged from AOR 1.4 (95% CI 1.0–2.0) (34) to AOR 2.00 ($P \leq 0.001$) (38) in longitudinal studies, and as high as AOR 2.18 (95% CI 1.84–2.59) in a cross-sectional study (analysis restricted to females only) (37). Significant correlations of 0.19–0.2 between sexual abuse and lifetime adolescent cannabis use by age 18 were also reported (39, 43). In longitudinal studies the non-significant effect estimates ranged from AOR 0.53 (95% CI 0.22–1.26) (44) to AOR 1.52 (0.98–2.36) (33). Notably, all the studies reporting a significant association relied on self-report of sexual abuse from participants and the majority of the studies that identified weaker evidence used child protection records of childhood sexual abuse to determine the exposure (33, 40, 41, 44). Six studies reporting AOR and 95% CI (33–35, 40, 42, 44) were entered into a meta-analysis, producing a weighted mean effect of OR 1.29 (95% CI 1.08–1.49) for the relationship between childhood sexual abuse and adolescent cannabis use.

For physical abuse, a significant association between the exposure and adolescent cannabis use was observed in 4 of the 7 studies which focussed on this form of abuse (36, 38, 41, 42), and weaker evidence was reported in 2 of the 7 studies (33, 40). One study (44) differentiated timing of abuse, and consequently reported both significant and non-significant findings dependent on the timing of exposure (see discussion in section Definition of Physical and Sexual Abuse). Significant effect estimates ranged from AOR 1.38 (95% CI 1.09–1.76) (42) to AOR 1.87 (95% CI 1.06–3.32) when exposure to abuse was in early adolescence (44) in longitudinal studies. A Beta of 0.62 (95% CI 0.25–0.99) was reported in a cross-sectional study (36). This stronger evidence for an association between physical abuse and adolescent cannabis use came from studies with both self-reported abuse and child protection records as outcomes. All of the studies providing weaker, non-significant evidence were longitudinal, and used child protection records as their exposure.

TABLE 2 | Data extraction.

References	Country	Study design	Measure of childhood abuse	% female	Mean age of sample (range)	Sample size	Cannabis use measure (lifetime, past year, frequency)	Statistical method	Univariable effect estimate (CI): composite measure of physical/ sexual abuse	Univariable effect estimate (CI): physical abuse	Univariable effect estimate (CI): sexual abuse	Covariate adjustment	Adjusted effect estimate (CI): composite measure of physical/ sexual abuse	Adjusted effect estimate (CI): physical abuse	Adjusted effect estimate (CI): sexual abuse	Notes
Chatterjee et al. (32)	USA	Cross-sectional	Self-reported, semi-structured scale	49.7	9th, and 11th grade	79,339	First use age 14 and under	Multivariable logistic regression analysis	na	na	na	Race/ethnicity, poverty status, grade, family composition, school location, and connexions to parents	Female 1.24 (1.04–1.43) Male 1.21 (1.03–1.42)	na	na	
Dubowitz et al. (33)	USA	Prospective cohort study	Child protective services records	Not specified	18 and under	702	Some use	Multinomial logistic regression analysis	na	na	na	Peer use, neglect, emotional maltreatment, extent of childhood maltreatment, sex, site, ethnicity/race	na	1.25 (0.80–1.95)	1.52 (0.98–2.36)	
	As above	As above	As above	As above	As above	As above	Heavy Use	Multinomial logistic regression analysis	na	na	na	Peer use, neglect, emotional maltreatment, extent of childhood maltreatment, sex, site, ethnicity/race	na	1.23 (0.72–2.08)	0.80 (0.47–1.37)	
Hayatbakhsh et al. (34)	Australia	Prospective cohort study	Self-reported	52.1	21	3,285	Occasional use	Multinomial logistic regression	___	___	SA Once or twice 1.7 (1.2–2.3) SA 3+ times 2.5 (1.7–3.9) Raped 2.2 (1.4–3.3)	Gender, mother's age, mother's education measured at the child's birth, family income, marital status and quality mother-child communication measured at 14 years, maternal anxiety, depression, smoking, alcohol consumption measured at 14 years, child internalising and externalising measured at 14 years	___	___	SA Once or twice 1.4 (1.0–2.0) SA 3+ times 2.1 (1.4–3.3) Raped 1.6 (1.0–2.6)	
	As above	As above	As above	As above	As above	As above	Frequent use	As above	na	na	SA Once or twice 2.2 (1.5–3.5) SA 3+ times 3.3 (1.9–5.7) Raped 2.7 (1.6–4.7)	Gender, mother's age, mother's education measured at the child's birth, family income, marital status and quality mother-child communication measured at 14 years, maternal anxiety, depression, smoking, alcohol consumption measured at 14 years, child internalising and externalising measured at 14 years	na	na	SA Once or twice 2.8 (1.7–4.4) SA 3+ times 3.6 (2.0–6.4) Raped 3.1 (1.7–5.8)	

(Continued)

TABLE 2 | Continued

References	Country	Study design	Measure of childhood abuse	% female	Mean age of sample (range)	Sample size	Cannabis use measure (lifetime, past year, frequency)	Statistical method	Univariable effect estimate (CI): composite measure of physical/ sexual abuse	Univariable effect estimate (CI): physical abuse	Univariable effect estimate (CI): sexual abuse	Covariate adjustment	Adjusted effect estimate (CI): composite measure of physical/ sexual abuse	Adjusted effect estimate (CI): physical abuse	Adjusted effect estimate (CI): sexual abuse	Notes
Hayatbakhsh et al. (35)	Australia	Longitudinal (MUSP), general population	Self-reported	34.3	21	3,754	Lifetime use	Multinomial logistic regression	na	na	Non-penetrative: 1.9 (1.4–2.5) Penetrative: 2.5 (1.8–3.5)	Gender, mother's age, changes in marital status, family income, problems in residential area, anxiety/depression, aggression/delinquency, nonverbal reasoning ability, school performance, puberty activity, child smoking, child alcohol use, TV watching, rule breaking at school, maternal smoking, maternal alcohol use, paternal history of crime, openness family communication	na	na	Non-penetrative: 1.7 (1.3–2.2) Penetrative: 1.8 (1.3–2.7)	
Hayre et al. (36)	Canada	Cross-sectional	Self-reported, semi-structured scale	59.3	12–18	528	Use in past month	Mediation sequential regression analysis	na	0.619 (0.245–0.993)	na	na	na	na	na	
Hébert et al. (37)	Canada	Cross-sectional school population	Self-reported, semi-structured scale	57.8	15.35 (grades 10–12)	8,194	Past year	Multivariable logistic regression analysis	na	na	na	Grade level, family structure, ethnicity. physical and emotional abuse, exposure to violence, exposure to interparental violence	na	na	Girls 2.18 (1.84–2.59) Boys 1.28 (0.88–1.84)	
Hussey et al. (38)		Prospective cohort study	Self-reported, structured, computerised	na	Grades 7–11	10,828	Last month	Binary logistic regression	___	1.65 $p \leq 0.001$	1.76 $p \leq 0.001$	Gender, age, race/ethnicity, parent's education, family income, immigrant generation, and US region	___	1.57 $p \leq 0.001$	2.00 $p \leq 0.001$	
Mason et al. (39)	US	Prospective cohort study	Interview, self-reported, childhood and adolescence	46	18	457	Life time	Path analysis	___	___	___	Mother's educational level, family after-tax income, mother's occupational level	___	___	r0.203 $p < 0.01$	
Mills et al. (40)	Australia	Prospective cohort study	State child protection agency records	52.6	21	3,778	Lifetime use	Logistic regression analysis	na	na	na	Age, gender, race, family income, maternal age, education, marital status, alcohol use, smoking, anxiety, depression	na	1.74 (0.91–3.34)	1.45 (0.77–2.72)	

(Continued)

TABLE 2 | Continued

References	Country	Study design	Measure of childhood abuse	% female	Mean age of sample (range)	Sample size	Cannabis use measure (lifetime, past year, frequency)	Statistical method	Univariable effect estimate (CI): composite measure of physical/ sexual abuse	Univariable effect estimate (CI): physical abuse	Univariable effect estimate (CI): sexual abuse	Covariate adjustment	Adjusted effect estimate (CI): composite measure of physical/ sexual abuse	Adjusted effect estimate (CI): physical abuse	Adjusted effect estimate (CI): sexual abuse	Notes
	As above	As above	As above	As above	As above	As above	Early initiation	Logistic regression analysis	na	na	na	Age, gender, race, family income, maternal age, education, marital status, alcohol use, smoking, anxiety, depression	na	2.59 (1.37–4.89)	2.11 (1.13–3.94)	
	As above	As above	As above	As above	As above	As above	Daily use	Logistic regression analysis	na	na	na	Age, gender, race, family income, maternal age, education, marital status, alcohol use, smoking, anxiety, depression	na	2.94 (1.24–6.99)	3.08 (1.14–8.29)	
Roberts et al. (41)	US	Prospective cohort study	Child protective services records	55.6	18	847	Last month	Multilevel linear models	na	na	na	Gender, race, exposure to maltreatment	na	Beta: 0.06, SE: 0.14	Beta: −0.23, SE: 0.16	
Scheidell et al. (42)	USA	Prospective cohort study	Self-reported, structured, computerised	54.3	Age 11–21	12,288	Lifetime use	Logistic regression analysis	na	1.89 (1.60–2.24)	1.69 (1.39–2.05)	Each other type of trauma, age, gender, race, and poverty	na	1.38 (1.09–1.76)	1.29 (0.97–1.71)	Only took adolescent wave results, as the other ages fell outside of the review age range
Watts et al. (43)	US	Cross-sectional	Self-reported, non-structured	100	Grades 7–12	670	Lifetime use	Analysis of variance	na	na	r0.185	na	na	na	na	Results only presented for females, consequently analysis sample N 670
Yoon et al. (44)	USA	Prospective cohort study	Child protective services records	52.9	ages 12–18	903	Past year cannabis use	Binary logistic regression	na	na	na	Gender, race, household income	na	Early childhood abuse: 1.72 (0.95–3.10) Adolescent abuse: 1.87 (1.06–3.32)	Early childhood abuse: 0.55 (0.25–1.21) Middle childhood abuse: 0.53 (0.22–1.26)	

The non-significant effect estimates ranged from AOR 1.25 (95% CI 0.80–1.95) (33) to AOR 1.74 (95% CI 0.91–3.34) (40). Four studies reporting adjusted odds ratios and confidence intervals (33, 40, 42, 44) were entered into a meta-analysis, producing a weighted mean effect of OR 1.39 (95% CI 1.12–1.66) for the relationship between childhood physical abuse and adolescent cannabis use.

Association Between Physical/Sexual Abuse and Age of Cannabis Initiation

Although not the primary focus of the review, some studies allowed an examination of the association between exposure to childhood maltreatment and age of onset of cannabis use. In a prospective cohort study, early onset of cannabis use (defined as prior to 17 years of age) was more than twice as likely amongst those who had experienced either physical abuse or sexual abuse (respectively, AOR 2.59, 95% CI 1.37–4.89 and AOR 2.11, 95% CI 1.13–3.94) (40). These effect estimates were significant, and stronger than for the association between either physical or sexual abuse and lifetime cannabis use (respectively, AOR 1.45, 95% CI 0.77–2.72 and AOR 1.45, 95% CI 0.77–2.72) (40). There was no clear linear pattern between sexual molestation and age of cannabis use in a cross-sectional study in U.S. school populations, with correlations reported by grade (7th−8th grade r0.19, 9th grade r0.03, 10th grade r0.15, 11th grade r0.09, 12th grade r0.35) (43), but it is notable that this study was rated low on quality.

Gender Differences in the Relationship Between Childhood Abuse and Adolescent Cannabis Use

Two cross-sectional studies provided separate estimates of the relationship between childhood physical/sexual abuse and adolescent cannabis use for males and females. Experiencing physical or sexual childhood abuse was associated with a significantly increased likelihood of cannabis use at age 14 or under for both males and females (32). Effect estimates were similar across genders, with an AOR of 1.24 (95% CI 1.04–1.43) for females and AOR 1.21(95% CI 1.03–1.42) for males. Experiencing sexual abuse was significantly associated with over twice the likelihood of past-year cannabis use in Canadian school grades 10–12 for females (AOR 2.18, 95% CI 1.84–2.59), but with only a slight and non-significant increase in likelihood for males (AOR 1.28, 95% CI 0.88–1.84) (37).

DISCUSSION

This review identified 13 papers reporting an association between childhood physical or sexual abuse and adolescent cannabis use (defined in the search as use up to age 26) (29). There was good evidence for a relationship between both physical and sexual abuse in childhood and increased likelihood of adolescent cannabis use in studies where abuse was self-reported. The reported range of effect sizes was similar for both physical and sexual abuse, indicating that those who experience these forms of childhood abuse may be around twice as likely to report adolescent cannabis use. However, evidence was weaker in studies where abuse was determined using child protection records. There were more papers reporting associations for sexual abuse than for physical abuse, and most of the thirteen selected papers for this systematic review had a quality rating that indicated lower risks of bias.

The range of effect sizes was similar for the association between both physical and sexual abuse and adolescent cannabis use. However, of the papers that did report both measurements, those with better quality ratings for lifetime use (40, 42), showed a stronger effect size for the association with physical abuse in comparison with sexual abuse. Physical abuse has been identified as a risk factor for adolescent drug use (20) and subsequent transition to use disorders (45), but the present results demonstrate that it has received less focus in the literature than sexual abuse (reported in 7 studies, compared to 11 for sexual abuse).

The review identified differences in the strength of the evidence for the relationship between childhood physical/sexual abuse and adolescent cannabis use were related to the method of ascertainment of abuse. In this sense, studies with data from child protective services should be interpreted carefully. Although the reliability of this source is high, detection of exposed individuals may be lower due to unreported cases to authorities. As some researchers (40) have previously observed, "rates of retrospective self-report of child maltreatment are generally much higher than rates of agency confirmation, which raises the possibility of maltreated youth being misclassified." Previous research has indicated that substantiated childhood maltreatment is no better at predicting outcomes than alleged (46). A recent review has identified that individuals who report abuse prospectively and retrospectively may represent different populations (47); consequently, it is important to compare differences between cross-sectional and prospective studies. In the present review cross-sectional and longitudinal designs were mostly in agreement, indicating that timing of reporting did not influence results.

Variations in exposure, such as the form and timing of the abuse, and the individual's gender may affect the relationship to adolescent cannabis use, but this is not widely explored in the literature. In the present review, one study (44) made a differentiation between early and middle childhood abuse, as well as adolescent abuse; only finding significant associations with past year cannabis use and physical adolescent abuse. Differences in the association with cannabis use were observed by frequency of the abuse and severity of the sexual abuse (34, 35). There were conflicting findings on whether effects may differ by gender (32, 40). Another recent review of this topic, focusing on cannabis abuse, also highlights the need for additional research on potential gender differences (19).

Adverse childhood experiences such as physical and sexual abuse are known to raise risks for life course negative mental health and addiction outcomes, and the present results indicate that adolescent cannabis use may be a plausible intervention target to mitigate these risks. A recent meta-analysis of the relationship between childhood physical/sexual abuse and adolescent cannabis abuse and dependence indicated that

cannabis abuse/dependence is more likely amongst those experiencing physical abuse (OR: 1.58, 95% CI 1.01–2.46), and more than twice as likely amongst those experiencing sexual abuse (OR: 2.35, 95% CI 1.64–3.35) (19). Similarly, a comprehensive meta-analysis indicated likelihood of experiencing depression or anxiety was more than twice as high amongst those reporting childhood physical abuse (OR 2.00, 95% CI 1.25–3.19) or sexual abuse (OR 2.66, 95% CI 1.88–3.75) (48), and similar results have been found in relation to the likelihood of reporting psychotic experiences in a longitudinal cohort (physical abuse AOR, 2.24 95% CI, 1.75–2.87, sexual abuse AOR, 2.04 95% CI, 1.42–2.91) (49).

Adolescent cannabis use is a necessary step in the progression to the development of cannabis abuse/dependence (24), and is a commonly identified risk factor for anxiety, depression and psychosis (9, 50). The results of the present review add to the evidence that preventing adolescent cannabis use may be a viable intervention target for reducing risks of these negative outcomes amongst those experiencing early adversities such as physical and sexual abuse.

LIMITATIONS

This review aimed to improve on previous studies by focussing the exposure to specific forms of adversity. However, a result of this approach was that we excluded studies which included composite measures of childhood abuse including non-physical abuses (e.g., emotional abuse and neglect). Future reviews may benefit from exploring the clustering of adversities. Our conclusions regarding sex differences and age of onset are weak considering the final number of studies that provided this information. To focus on cannabis use, distinct from abuse or dependence, studies of problematic use were excluded. However, this may have precluded us from identifying variation in frequency of use, which is an important consideration in the development of addiction and mental health. Studies did not commonly report unadjusted odds ratios, with the result that odds ratios included in the meta-analysis of weighted average have different adjustment patterns. A further limitation of the meta-analyses was the exclusion of studies that did not report odds ratios. Finally, we limited the search to studies published in the English language which may have excluded some relevant literature.

CONCLUSIONS

There is some evidence both physical and sexual abuse may represent important risk factors for adolescent cannabis use. Adolescent cannabis use precedes the development of dependence, and is strongly associated with increased risk of negative mental health outcomes; further exploration of adolescent cannabis use's place on the causal pathway between childhood abuse and adult addiction and mental health problems is warranted to improve intervention.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

VD, LH, and ML developed the concept and scope of the paper. VD and LH produced the search strategy. VD and SN ran searches, screened papers, and completed quality rating and data extraction. LH oversaw these processes and resolved any conflicting decisions. VD drafted the manuscript, and LH performed meta-analyses. All authors made substantial contributions to the interpretation of the data and contributed to revising the manuscript critically. All authors approved the final version of the study to be published and are accountable for all aspects of the work.

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Cannabis Use and Car Crashes: A Review

Ulrich W. Preuss[1,2], Marilyn A. Huestis[3], Miriam Schneider[4], Derik Hermann[5], Beat Lutz[6], Alkomiet Hasan[7], Joseph Kambeitz[7], Jessica W. M. Wong[8] and Eva Hoch[7]*

[1] Vitos Klinik Psychiatrie und Psychotherapie, Herborn, Germany, [2] Department of Psychiatry, Psychotherapy and Psychosomatics, Martin-Luther University Halle-Wittenberg, Halle, Germany, [3] Institute on Emerging Health Professions, Thomas Jefferson University, Severna Park, MD, United States, [4] Institute of Psychology, Heidelberg University, Department of Developmental and Biological Psychology, Heidelberg, Germany, [5] Department of Addictive Behaviour and Addiction Medicine, Central Institute of Mental Health, Mannheim, Germany, [6] Institute of Physiological Chemistry and German Center for Resilience, University Medical Center of the Johannes-Gutenberg-University Mainz, Mainz, Germany, [7] Clinic and Polyclinic for Psychiatry and Psychotherapy, Clinic of the Ludwig-Maximilian-University Munich, Munich, Germany, [8] Am Homberg Clinic, Bad Wildungen, Germany

In this review, state-of-the-art evidence on the relationship between cannabis use, traffic crash risks, and driving safety were analyzed. Systematic reviews, meta-analyses, and other relevant papers published within the last decade were systematically searched and synthesized. Findings show that meta-analyses and culpability studies consistently indicate a slightly but significantly increased risk of crashes after acute cannabis use. These risks vary across included study type, crash severity, and method of substance application and measurement. Some studies show a significant correlation between high THC blood concentrations and car crash risk. Most studies do not support this relationship at lower THC concentrations. However, no scientifically supported clear cut-off concentration can be derived from these results. Further research is needed to determine dose-response effects on driving skills combined with measures of neuropsychological functioning related to driving skills and crash risk.

Keywords: cannabis, cannabinoids, THC, automobile driving, impaired driving, driving safety, driving skills, driving ability

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****Correspondence:***
Ulrich W. Preuss
ulrich.preuss@medizin.uni-halle.de

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INTRODUCTION

Cannabis is worldwide the most frequently used illicit drug (1). Rates of driving under the influence of cannabis rose in recent years (2). For instance, the DRUID (Driving Under the Influence of Drugs, Alcohol and Medicines) project reported on 50,000 drivers from 13 different countries of whom 1.32% used cannabis (3). On weekends, the rates of positively screened cannabis users in traffic were 10–12% and in subjects involved in a car crash 26–27% (3, 4), while 0.5–7.6% of persons involved were severely injured.

"Cannabis-impaired driving" describes the impairment caused by cognitive and psychomotor effects of Δ9-tetrahydrocannabinol (THC) which negatively influences a driver of a motor vehicle after THC consumption. In contrast, a "cannabis-positive driver" is someone driving a motor vehicle with any detectable THC concentration in blood, oral fluid, or urine with/without showing impairments in his driving. "Driving under the influence of cannabis" (DUIC) is a judicial term which refers to a driver exhibiting a measured reduction in cognitive or psychomotor skills in conjunction with a defined THC concentration in blood, oral fluid, or urine (5).

THC acutely and probably chronically reduces different cognitive and psychomotor abilities needed for driving, like balance, executive function, motor impulsivity and impulse control, perception, psychomotor speed, short-term memory, visual processing, and working memory (reaction time and accuracy) (3, 6). All these reductions may be dose-dependent (4), negatively influence driving skills and car crash risk, and may worsen with duration and frequency of cannabis use (5). However, results on the relationship between driving performance and traffic crash risk under the influence of cannabis revealed inconsistent findings (6–8).

Methodological heterogeneity may explain mixed findings. As summarized by Asbridge et al. (2), several study types need to be considered for a comprehensive evaluation of the relationship between cannabis use, driving skills, and car crash risk [e.g., sample surveys, laboratory experiments, and epidemiological studies like case-control and their variant, "culpability" studies (2, 7)]. Each of the study approaches has strengths and weaknesses. For instance, it is challenging in epidemiological studies to obtain the proportion of cannabis users in their samples. Some studies rely on self-reports which may underestimate the actual fraction of cannabis users. Only a minority of all studies assesses cannabis content in blood or other body tissues or fluids at the time of the crash. However, it may be unclear whether the cannabis consumption is occasional or frequent, or when the last cannabis intake occurred prior to the crash. Among other factors which may contribute to crash risk under the influence of cannabis are the use of additional substances (e.g., alcohol) and the frequency and chronicity of cannabis use. Again, only a fraction of studies reports a combined assessment of various legal and illicit substances or controls for other confounding factors (7).

Timing of cannabis use prior to an event and frequency of cannabis use have different effects on driving skills. While laboratory and experimental studies are often of small sample size, they usually assess specific driving impairment under various but defined doses of smoked or oral cannabis products (6) in an artificial environment with participants themselves aware of possible impairments from cannabis use who tried to compensate with slower and less risky driving (6).

These laboratory investigations are complemented by a recent double-blind, randomized clinical trial on $n = 26$ healthy occasional cannabis users (9) which were exposed to vaporized THC-dominant, CBD-dominant, THC/CBD-equivalent, and placebo cannabis. The end point measured was standard deviation of lateral position (SDLP; a measure of lane weaving) during 100 km on-road driving tests 40 and 240 min after cannabis consumption.

The SDLP following vaporized THC-dominant and THC/CBD-equivalent cannabis vs. placebo was shown to be significantly greater at 40–100 min but not 240–300 min, but there were no significant differences between CBD-dominant cannabis and placebo. The doses tested here may be representative of common usage.

In comparison, epidemiological and survey samples are frequently not assessed regarding their neuropsychological impairments which may lead to heterogeneity of study results. Not surprisingly, some studies which analyzed the association between use of cannabis and the risk of car vehicle crashes reported an increased risk (10–12), while others reached inconclusive results (13, 14).

Different study types have various outcome criteria. Some of the meta-analytical studies included crashes with injuries and fatalities (2) while others included simple collisions (6, 15), all of which have a different profile of risk factors. Also, five meta-analyses summarized the effect size of DUIC (2, 6, 15–17) and suggested that the risk of vehicle crashes is increased by cannabis. All studies used a random-effect model to assess the effect size of cannabis use on car crashes. However, all studies also reported a significant heterogeneity across analyzed studies. The more recent meta-analysis reported that the significant heterogeneity found was caused by publication bias favoring studies showing a positive association between DUIC and car crash risk (15).

In summary, one study approach alone may be insufficient to assess driving skills and traffic offenses in DUIC due to a variety of confounding and methodological factors.

RESEARCH QUESTIONS

This review has three purposes. First, we searched the scientific evidence for a link between the use of cannabis, driving safety, and risk of car crashes by concentrating on recent meta-analyses and large case-control-studies. Second, we evaluated the role of sample subgroups (e.g., role of co-consumed alcohol), study types (e.g., case control vs. culpability), and kind of crash (collision, injury, fatality) regarding DUIC and car crash risk. Third, independent of meta-analyses, we wanted to clarify the relationship between car crashes and different concentrations of THC detected in blood or other body fluids of drivers.

METHOD

This review is part of an expert report [Cannabis: Potential and Risks: A scientific analysis (CaPRis)] funded by the German Ministry of Health (18). It followed guidance of the Cochrane Collaboration (19). Other parts of this report have been published earlier (20). The study protocol can be found at: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016033249.

Rationale

In accordance with the German Association of the Scientific Medical Societies (AWMF) (21) this review followed a top-down search strategy. We prioritized studies with the highest level of evidence, i.e., aggregated data in systematic reviews and meta-analyses according to PRISMA (22). If our first search failed to answer the clinical questions, we then included studies with a lower level of evidence (e.g., cohort studies, case control studies). PubMed, PsycINFO, Medline, Embase, and the Cochrane Library were systematically searched. References of the identified reviews and meta-analyses were manually searched to identify additional studies. Researchers in this field were contacted. Screening of the search results, assessing eligibility and methodological quality of full-text articles, data extraction, and data synthesis were

independently performed by two reviewers; disagreements were resolved through consensus or referral to a third expert.

Eligibility Criteria

The inclusion criteria were systematic reviews or meta-analyses and prospective cohort studies investigating the effects of cannabis use on cognition, intelligence, driving performance, and traffic crashes. All studies published in English or German from 2005 to 2020 were considered. Outcome criteria wasn't specified. Exclusion criteria were non-systematic reviews, reviews without documented systematic literature search, systematic reviews not focusing on cannabis/cannabinoids, animal and molecular studies, expert opinion, and position statements.

Search Strategy and Methodological Assessment

For the global search, terms (MeSH-Terms) used were: "Cannabis OR cannabinoid* OR hemp OR hanf" OR 2) "Mariuana OR Marihuana OR Marijuana." Search strings were built, pilot-tested, and adopted to different databases. All studies included were rated for their methodological quality using the SIGN-checklist (23) revealing scores ranging from "high quality (++)," "acceptable quality (+)," "low quality (–)," to "unacceptable – reject." Each study was rated on its level of evidence, based on study type and quality (24) ranging from "1" (highest level of evidence) to "5" (lowest level of evidence).

Data Synthesis

This review applied a qualitative data synthesis approach. An aggregated data analysis couldn't be used because of the high heterogeneity of primary outcome measures. The study results were interpreted with respect to their sample size, level of evidence, risk of bias, and level of heterogeneity/homogeneity. If there was a case of duplicate primary studies, the following preference criteria was included (23): the availability of numerical data or results; the highest SIGN-rating (Quality assessment tool for systematic reviews); most recent date of publication; larger number of studies and observations. Assessments were made independently for each outcome. If two reviews with duplicate primary studies reported on different outcomes, both were eligible for inclusion.

RESULTS

The global literature search identified 470 publications across all databases. After removal of duplicates, 272 manuscripts remained and were screened for eligibility (**Figure 1**). The literature search on cannabis, driving skills, and related crash risks resulted in 14 publications of which three were not systematic reviews (1, 3, 6) and one report was not included for further analyses (25) because it did not report on driving skill characteristics. Three studies (2, 7, 15) reported meta-analytic results on cannabis use and car accidents and were considered for inclusion. Two subsequent studies were published after the CAPRIS literature search (15, 17) and were also included. To evaluate the relationship between THC blood concentrations and crash risk, five large case-control (culpability) studies were included (26–30). According to the included study designs, the evidence was rated 3 as "good to moderate" quality (24).

Results of Meta-Analyses

Asbridge et al. (2) conducted the first meta-analysis, which we rated as "high" for its methodological quality ("++") according to SIGN (23). It included four studies on traffic accidents and injuries, and five studies on fatalities related to cannabinoid use. The authors used the Newcastle-Ottawa-Scale (31) for the assessment of retrieved studies. Their screenings resulted in a "high"-rating for four and a "moderate"-rating for five of these studies. In eight of the nine included studies, THC was analyzed in whole blood, serum, or plasma while one included study (10) relied on self-reported use. Seven of the nine included studies reported significantly increased traffic crash risk in individuals up to 1 h after cannabinoid use. Overall meta-analytical statistics demonstrated an OR of 1.92 (95% CI 1.35–2.73, **Table 1**) for crashes after cannabis use and thus almost doubled the risks compared to controls, after weighting the studies. Hence, heterogeneity of results and research designs across the nine studies were substantial. Studies which received "moderate" quality rating reported a lower car crash risk (OR of 1.78) compared to those with "high" quality ratings (OR 2.21). Furthermore, case-control studies had significantly higher OR for traffic crashes following cannabis use (OR = 2.79; 95% CI: 1.23–6.33) than culpability studies (OR = 1.65; 95% CI: 1.31–3.36, **Table 1**). Additional analyses revealed that traffic crash risk is increased in both fatal and non-fatal cases after cannabinoid consumption while fatal cases only achieved statistical significance (fatal crashes OR 2.1; 95% CI 1.31–3.36 vs. non-fatal crashes OR 1.74; 95% CI 0.88–3.46).

The meta-analysis of Li et al. (16) received an "acceptable" ("+") quality rating according to SIGN (23). Nine studies were included in their analyses of which six investigated non-fatal and one fatal car crashes while two investigated both fatal and non-fatal car crashes under the influence of cannabis. Study types considered in this meta-analysis included case-control, cross-sectional, and cohort studies. Five of the nine studies assessed marijuana use based on self-reported data, and 2 were based on urine, one on blood, and one on both urine and blood tests. Eight of the nine studies reported an increased traffic crash risk after cannabis use except for one report from Thailand (32). Results of the meta-analysis demonstrated a statistically significant OR of 2.66 (95% CI 2.07–3.41, **Table 1**) after weighting study results. Most results stayed significant after controlling for several confounding factors like alcohol intake, while adjusted ORs decreased after statistical correction. However, heterogeneity of results also achieved statistical significance. Secondary analyses revealed that study designs, methods of drug testing, or age of study participants influenced outcomes. It is important to note that studies had variable approaches to assess cannabis use before driving. While cross-sectional and case-control studies limited cannabis use by self-report and laboratory tests between 1 and 3 h before driving, cohort studies relied on self-reports of current and last year's cannabis use. Further, in their analyses, OR for several potentially confounding factors were determined. Cross-sectional studies (two studies) had the highest crash risk

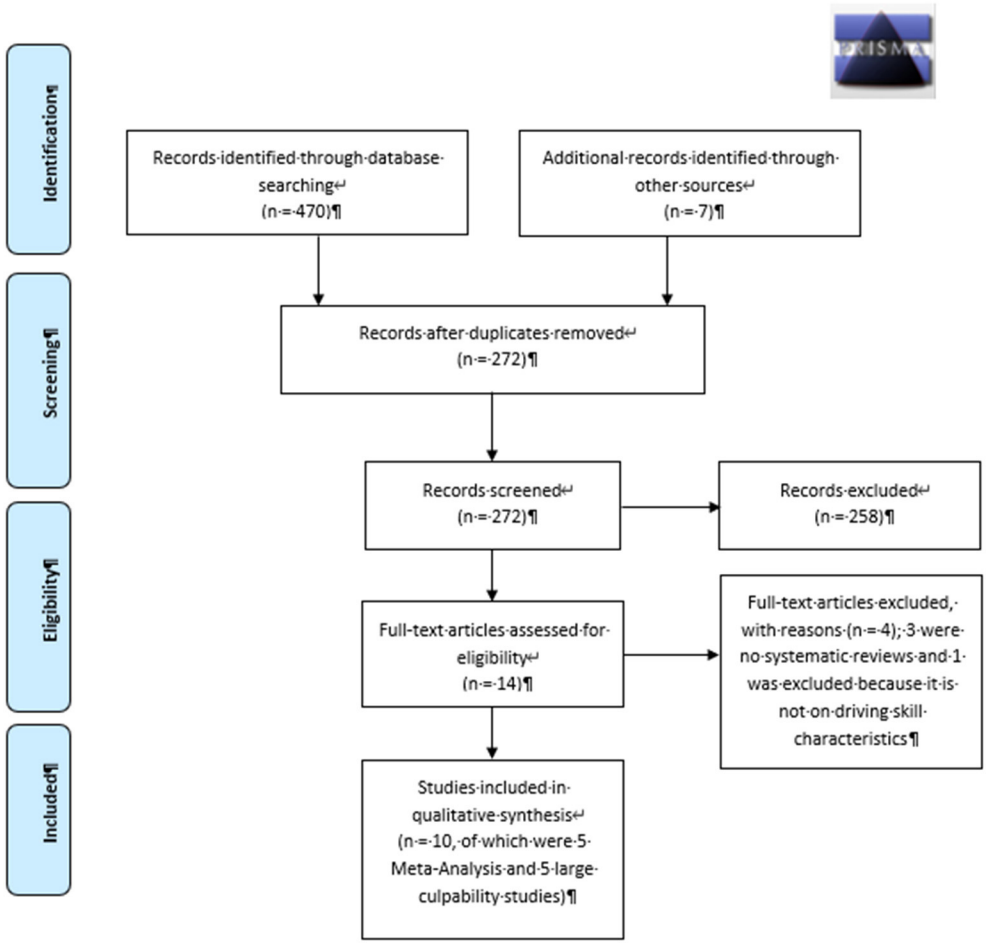

FIGURE 1 | Prisma flow diagram cannabis use and car crash risk (see also Results section).

(OR 3.61), followed by case control-studies (five studies) (OR 2.63) and cohort studies (two studies, OR 2.04). Estimated ORs of self-reports were increased in comparison to blood or urine testing (2.93 vs. 2.26) as well as studies in subjects aged under 25 years (3.03) vs. other age groups (2.50). Moreover, five of the nine studies reported co-use of alcohol, but ORs are not reported.

Elvik (7) included the largest research with 27 studies from Europe, USA, Canada, Australia, New Zealand, and Thailand. It received a "high" quality rating ("++") according to SIGN (23). Study types included were case-control (ten), culpability (nine), epidemiological (seven), and cohort investigations (one). Twenty studies assessed drug use in terms of the results of laboratory analyses of blood or saliva, but it is unclear from the analyses how many studies investigated blood or saliva or other body fluids, like urine.

These studies had a low to moderate methodological quality which was due to differences in controlling for potential confounding variables. Meta-statistics estimated ORs of severity of the crash and computed ORs separately for fatal crashes as well as for injuries and property damage. Cannabis use increased the risk for traffic crash up to 50% while the risk for a fatal crash had an OR of 1.31 (95% CI 0.91–1.88, insignificant, 1.26, 0.88–1.81 after adjusting for publication bias). Car crashes with injuries resulted in an OR of 1.26 (95% CI 0.99–1.6, 1.10, 0.88–1.39) while the risk for crash-related property damage was significantly increased (OR 1.48, 95% CI 1.28–1.72) which remained significant after controlling for publication bias (OR 1.26, 95% CI 1.1–1.44, **Table 1**). Risk for severe injuries in crashes was higher in studies with self-reported cannabis use (OR = 1.31; 95% CI: 0.8–2.15) vs. laboratory screenings of body fluids (OR = 1.16; 95% CI: 0.79–1.71). In this meta-analysis, again, quality of included studies had a significant effect on outcome ORs. A numerical index of study quality was developed and found that studies with high index scores sometimes reported lower estimates of risk than studies with low index scores (12). It remains unclear which of the studies included in the meta-analysis were of "low" and "high" quality.

Rogeberg and Elvik (17) conducted a meta-analysis on two study samples. The first analysis replicated previous work (2, 16), which the authors found hard to interpret (17).

After re-analysis of the Asbridge study, adjusted OR estimates of 1.25 (95% CI 1.0–1.55) were found (from previously reported 1.95, 1.35–2.73) and for the Li et al. study, adjusted OR was ∼1.55 (95% CI 1.10–2.20, from 2.66, 2.07 to 3.41, previously reported).

In the second meta-analysis, 21 observational studies were included. Revised estimates were in a similar range as the adjusted ORs of study 1 (re-analyses of Asbridge et al. and Li et al. data). A statistically significant increase in risk of low-to-moderate magnitude OR 1.36 (1.15–1.61) was reported from the mixed model and an OR of 1.22 (1.1–1.36) in the meta-regression model.

Subsample analyses found relatively higher OR estimates for case–control studies OR 1.36 vs. culpability OR 1.12, low OR 1.45 vs. high quality OR 1.39, no limited control of confounders OR 1.52 vs. high confounder adjustment OR 1.17, and not controlling for alcohol intoxication OR 1.79 vs. controlling OR 1.11. In general, OR estimates of the relationships between cannabis use and car crash risk and subgroups are somewhat lower than those reported from previous meta-analyses (17).

Hostiuc et al. (15) employed two meta-analytical statistical approaches of DUIC and traffic crash risk. These approaches included a random-effects and inverse variance heterogeneity model to assess statistical significance of effect sizes. Altogether, $n = 24$ studies were included into the analyses, of which $n = 10$ relayed on blood analyses (one blood, urine and saliva, two on blood and self-report, one urine and blood, one saliva and blood combinations), $n = 10$ on self-report only (one additional study on self-report and saliva), one on urine analyses and two on "official databases." Crash risk in DUIC tested via blood analyses had an OR of 1.97, fatal accidents reached an OR of 1.56, and self-reports an OR of 1.94, while the overall effect size for DUIC and crash risk was not statistically significant. Across study types, again, case-control studies presented a higher OR (1.99) than other study types (1.81). Moreover, risk of crashes with injury (OR 2.18) in DUIC and collision (OR 1.81) were higher than those for fatal car crashes (OR 1.73). Using the alternative statistical model, OR estimates were generally 0.2 lower (**Table 1**). The authors considered several possible causes for their results in the meta-analysis, including heterogeneity of study types and assessment methods. Indeed, no association between DUIC and crash risk and a lack of sensitivity of their statistical approach (random effects model) was found. In addition, publication bias was remarkably high, but rather toward studies reporting a positive association between DUIC and crash risk. To homogenize and focus research on this topic, the authors suggested corroboration with objective data on cannabis use (like blood analyses, with clear cut-off values), or a clinical assessment of the impairment, in the event of a positive screening in traffic, before assessing the individual's fitness to drive (15).

Relationship Between Different THC Blood Concentrations and Car Vehicle Crashes

Five large case-control studies (26–30) assessed the link between THC blood concentration and crash risk.

Drummer et al. (26) investigated $n = 3{,}398$ fatal crashes under the influence of alcohol and drugs from three Australian states, including alcohol- and substance-free controls. Using logistic regression analyses; influence of alcohol, cannabis, and other substances; and other factors like age and gender on likelihood of culpability were determined. Drivers with blood THC concentrations of 5 ng/ml or higher showed greater and more statistically significant odds ratio (OR 6.6, 95% CI 1.5–28.0) (**Table 2**). The estimated odds ratio is greater than that for drivers with a blood alcohol concentration (BAC) of 0.10–0.15% (OR 3.7, 95% CI 1.5–9.1). A significantly positive association with culpability was seen with drivers positive to THC and with BAC $\geq$ 0.05% compared to those with BAC $\geq$ 0.05% alone (OR 2.9, 95% CI 1.1–7.7).

The same authors recently conducted a culpability study to include 5,000 injured motor vehicle drivers with comprehensive blood toxicology testing (30). The sample included 1,000 drivers for each of 5 years from ∼5,000 to 6,000 drivers injured and taken to hospital in the State of Victoria, Australia. A comprehensive blood-testing was conducted. In a logistic regression, drivers under the influence of THC showed a modest increase in culpability odds, when concentrations of all assessed substances were considered vs. controls (OR 1.9, 95% CI 1.2–3.1, $p = 0.007$). The increase in odds was most obvious at higher blood THC concentrations. At 5 ng/mL and above the OR was 3.2 ($p = 0.01$), and at THC concentrations of 10 ng/mL and above the OR was 10 ($p = 0.03$). At 1–5 ng/ml, the OR was 1.6 (95% CI 0.9–2.7), 5–9 ng/ml 1.9 (95% CI 0.7–5.0), 5 ng/ml and above the OR was 3.2 (95% CI 1.3–7.2, $p = 0.01$), and at THC concentrations of 10 ng/mL and above the OR was 10 (95% CI 1.3–82, $P = 0.03$). These results indicated increasing odds of culpability with rising concentration. THC was the third most prevalent drug detected in 11.1% of all drivers, following alcohol and stimulants. Only 1% of the 5,000 drivers had THC-only at 10 ng/mL or higher. The authors conclude that their culpability analysis of almost 5,000 injured drivers provided further evidence that elevated odds of culpability correlate with increasing THC levels, particularly those with higher blood concentrations.

Laumon et al. (27) conducted a case-control study on cannabis intoxication and fatal road crashes in France. They analyzed $n = 10{,}748$ drivers, with known drug and alcohol concentrations, involved in fatal crashes in France from October 2001 to September 2003. A total of 6,766 of these were considered culpable at the crash while $n = 3{,}306$ drivers served as controls. In addition, $n = 681$ drivers were positive for cannabis (cases 8.8%, controls 2.8%), including 285 with an illegal blood alcohol-concentration ($\geq$0.5 g/l). Positive cannabis detection was associated with increased risk of responsibility (OR 3.32, 95% CI 2.63–4.18). A significant dose effect was identified; the odds ratio increased from 2.18 (1.22–3.89) for $0 <$ THC < 1 ng/ml to THC ≥ 5 ng/ml OR 4.72 (3.04–7.33), uncorrected. The effect of cannabis remains significant after adjustment for different cofactors, including alcohol, with which no statistical interaction was observed (**Table 2**). At least 2.5% (1.5–3.5%) of fatal crashes were estimated as being attributable to cannabis, compared with 28.6% for alcohol (26.8–30.5%). The authors concluded that driving under the influence of cannabis increases the risk of involvement in a fatal car crash, while

TABLE 1 | Meta-analyses of driving under the influence of cannabis (DUIC) and risks of car vehicle crash studies.

References	*N* participants	*N* studies	Odds ratio selected outcomes	95% CI	SIGN
Hostiuc et al. (15)	$n = 245{,}591$	24 studies	REM:		++
			All: 1.89	1.58–2.26	
			Collision: 1.95	1.24–3.05	
			Injury: 2.16	1.41–3.28	
			Fatal: 1.73	1.36–2.19	
			Case-control: 1.95	1.51–2.51	
			Other studies: 1.81	1.38–2.39	
Rogeberg and Elvik (17)			REM		+
	$n = 50{,}877 +$	9 + 9 studies	All: 1.36	1.15–1.61	
	$n = 93{,}229$	21 studies	Fatal 1.32	1.08–1.62	
	$n = 239{,}739$	(re-analysis)	Case Control 1.60	1.19–2.15	
Elvik (7)		27 studies	REM		++
			Property damage: 1.26	1.10–1.44	
			Injury: 1.10	0.88–1.39	
			Fatal 1.26	0.88–1.81	
			Self-report:1.31	0.80–2.15	
			Lab Tests: 1.16	0.79–1.71	
Li et al. (16)	$n = 93{,}200$	9 studies	REM		+
			All: 2.66	2.07–3.41	
			Case-control: 2.63	1.87–3.71	
			Cohort: 2.04	1.36–3.07	
			Cross-sectional: 3.61	2.37–5.49	
			Self-report: 2.93	2.07–4.17	
			Blood/urine test: 2.26	1.46–3.49	
Asbridge et al. (2)	$n = 51{,}783$	9 studies	REM		++
			All: 1.92	1.35–2.73	
			Case-control: 2.79	1.23–6.33	
			Culpability: 1.65	1.11–2.46	
			Fatal: 2.10	1.31–3.36	
			Non-fatal: 1.74	0.88–3.46	

CI, confidence interval; SIGN Methology Checklist: High quality (++), acceptable (+), unacceptable (–), reject (0); REM, random effects model.

the risk in their study was lower than that with positive blood alcohol concentrations.

Martin et al. (28) conducted a similar French cohort study more than a decade later. The authors included $n = 4{,}059$ drivers. More than 300 of their characteristics, including DUIC and fatal crash risk, were obtained. The proportion of persons driving under the influence of alcohol was 2.1% (95% CI: 1.4 ± 2.8) and under the influence of cannabis 3.4% (2.9–3.9%). Drivers under the influence of cannabis multiplied their risk for causing a fatal crash by 1.65 (1.16 ± 2.34). Strength of the study is certainly its presentation of separate crash ORs for various doses of cannabis detected in blood samples, after adjusting for age, gender, vehicle category, and time of crash, which replicated results from a previous publication of the same research group (27) and the Australian study (26) (**Table 2**). Another finding of the second French sample is that there was no significant alcohol × cannabis interaction. This means that the increased risk of a fatal crash due to alcohol does not differ significantly from driving under the influence of cannabis (and vice versa).

Brubacher et al. (29) recently conducted a responsibility analysis in a case-control sample to determine whether drivers injured in motor vehicle collisions who tested positive for THC or other drugs are more likely to have contributed to the crash than those who tested negative. Participants included $n = 2{,}318$ injured drivers who required blood tests for clinical purposes following a motor vehicle collision, of whom 8.3% were screened positively for THC and 14.4% for alcohol. In addition, excess whole blood remaining after clinical use was obtained and broad-spectrum toxicology testing performed. To analyze data, unconditional logistic regression to determine ORs of crash risk for drivers with $0 < \text{THC} < 2$ ng/ml, $2\,\text{ng/ml} \leq \text{THC} < 5$ ng/ml and $\text{THC} \geq 5$ ng/ml (all vs. $\text{THC} = 0$ ng/ml). Risk estimates were adjusted for age, gender, and presence of other impairing substances. Odds ratios for all three ranges of blood tested THC were low (**Table 2**) and not statistically significant. Alcohol × Cannabis interactions were detected for pos. BAC × $\text{THC} < 2$ ng/ml OR = 1.75 (0.37, 17.1) and × $\text{THC} \geq 2$ ng/ml OR = 1.62 (0.34, 15.7) which did not reach statistical

TABLE 2 | Case control studies of fatal traffic injuries dividing drivers into culpable (or responsible) cases and non-culpable cases.

References	Country	*N*	THC in blood ng/ml	Odds ratio†; * - ****	Confidence interval	SIGN****	Body tissue or fluid analyzed
Drummer et al. (30)	Australia	5,000 drivers injured as a result of a vehicular collision	THC (all concentrations)	1.9****	1.2–3.1	++	"Blood samples"
			THC 1–4.9	1.6****	0.9–2.7		
			THC 5–9.9	1.9****	0.7–5.0		
			THC ≥ 5	3.2****	1.3–7.2		
			THC ≥ 10	10****	1.3–8.2		
Brubacher et al. (29)	Canada	2,318 non-fatally injured motor vehicle drivers	THC = none detected	Reference		++	"Whole blood samples"
			0 < THC < 2	1.09***	0.63–1.92		
			2 ≤ THC < 5	1.16***	0.66–2.13		
			THC ≥ 5	1.74***	0.59–6.36		
			Any THC	1.13†	1.03–1.28		
Martin et al. (28)	France	4,059 fatal accidents	Any (≥1)	1.65**	1.2–2.3	++	"Blood concentration of THC of over 1 ng/ml"
			THC < 1	1**			
			THC 1–3	1.4**	0.9–2.1		
			THC 3–5	3.6**	1.4–9.5		
			THC ≥ 5	1.6**	0.9–3.0		
Laumon et al. (27)	France	10,748 fatal traffic crashes while driving under the influence of cannabis	Any	Reference	1.4–2.3	++	"Blood concentration of THC of over 1 ng/ml"
			THC < 1	1.6*	0.8–3.0		
			THC 1–2	1.5*	1.1–2.2		
			THC 3–4	2.1*	1.2–3.7		
			THC ≥ 5	2.1*	1.3–3.4		
			Any dose	1.78*	1.4–2.3		
Drummer et al. (26)	Australia	3,398 fatal accidents	Any THC	2.7	1.02–7.0	++	Blood (post mortem)
			THC ≥ 5	6.6	1.5–28.0		

**Included variables: blood concentration of delta-9-THC, blood concentration of alcohol, age, vehicle type, time of crash.*

***Included variables: age, gender, vehicle category, time of accident.*

****Logistic regression with adjustment for age, sex, health authority, cannabis, alcohol, other recreational drugs, and sedating medications. † Unadjusted model.*

*****Logistic regression with adjustment for gender, age group, type of vehicle (car/motorbike/heavy vehicle/van or light truck) and location (metro/rural).*

SIGN Mythology Checklist: High quality (++), acceptable (+), unacceptable (–), reject (0).

significance. Unadjusted OR for car crash risk under any THC blood level was 1.13 (1.03–1.28). This study, like other culpability and case control studies, relied on blood samples instead of self-reports. Additional strengths are the assessment of alcohol and recreational drug use. However, in comparison to the three previous case-control/culpability studies which included fatal crashes, non-fatal motor crashes with injuries only were analyzed in this study (29).

DISCUSSION

In this review we first analyzed the general relationship between any crashes in DUIC chronic cannabinoid use, and second, how this relationship changes when potential co-factors are considered. The research on these topics includes five meta-analyses on several study types (case-control, culpability, and cohort studies) (2, 7, 15–17).

All five meta-analyses agreed that cannabinoid use is related to a higher traffic crash risk. However, the OR estimates and 95% CI and statistical significance across studies are variable (**Table 1**), while the number of included studies unsurprisingly increase over time. The initial meta-analysis (2) analyzed nine studies with $n = 51{,}783$ participants, the second meta-analysis from the same year (16) also included nine studies with $n = 92{,}200$ individuals. In this second meta-analysis (16), only two studies (9, 31) were previously analyzed (2). The third meta-analysis (7) with 27 studies included eight studies each of the first (2) and second (16) meta-analysis, while 12 studies were added. Rogeberg and Elvik (17) re-analyzed data from the first and second meta-analysis (2, 16) and added a second study with 21 included investigations, of which $n = 14$ were also analyzed in the previous study of Elvik (7). The most recent analysis (15) included 24 studies, of which 12 were analyzed in the hitherto largest meta-study (7). Thus, there is some, but not complete, overlap of studies included into available meta-analytical research on this topic. Selection criteria also vary across studies. Some include case-control and culpability studies (2, 17) or in addition cohort (16) or laboratory studies (7) and eventually case-control, culpability, survey, and cohort studies (15).

All meta-analyses noted significant heterogeneity across included studies [Asbridge et al. (2): I2: 81; Li et al. (15): heterogeneity: Q = 38.21; $P < 0.0001$; I2 ¼ 79.1; Elvik (7): test for heterogeneity "positive" for all outcomes; Rogeberg and Elvik (17): "there is heterogeneity across studies;" Hostiuc et al.

(15): overall Q = 216,59, $p < 0.001$; I2 = 90%]. The last study also presented heterogeneity statistics for several outcome criteria [collision subgroup Q = 47,06, $p < 0.001$, I2 89%; injury subgroup Q = 62.0; $p < 0.001$, I2 82%; fatal Q = 19.26, $p < 0.001$, I2 79% (15)].

All these factors may explain why there is some variation in the OR estimates across meta-analyses for the overall statistics. Further, case-control studies reach higher OR estimates than culpability studies and, except for (2), fatal crashes lower OR estimates than other kinds of crashes. Finally, studies based on self-reports have higher ORs than those based on blood or urine results. Culpability studies (2) include drivers involved in collisions, sub-grouped into those responsible for the collision and those not responsible. The premise of these studies is, if cannabis use increases collision risk, then it should more likely be detected in drivers judged to be responsible for their collision. However, OR may be higher in case-control studies, where DUIC subjects are compared to non-DUIC controls. Further, DUIC may impair driving skills and increase crash risk, however, risk of fatal crashes is lower than other types of crashes (collision only, injury). Thus, the increased risk for car crashes is relatively higher for collision and injury and somewhat attenuated but still increased for fatalities.

Self-reports of cannabis use may be subject to recall bias and may be less precise to detect actual cannabis use compared to blood or urine tests. Usually, it is assumed that cannabis use is underestimated in self-reports. As commented in previous analyses (16) different methods of assessing cannabis use (e.g., self-report, urine tests, and blood tests) may have different levels of validity and reliability. The authors of one meta-analysis (17) stated that, to their view, laboratory analyses of blood samples for all subjects included in a study provide the best information on acute intoxication while driving. The second best indicator is saliva. Urine is a less informative indica tor, as inactive metabolites of cannabis can be detected in samples of urine a long time after the substance became inactive.

Most of these screenings determine whether cannabis was used within the past few weeks, whereas acute impairment in driving skills from cannabis use lasts between 3 and 12 h (16, 33). Cannabis being an illicit drug in most countries, drivers in the comparison groups might be less likely than those involved in crashes to submit to testing, which could lead to overestimation of the effect of marijuana use on crash risk.

These meta-analyses have several limitations. The fourth meta-analysis (17) found only five studies that calculated crash risk for drivers with blood THC > 2 ng/ml. Further, all case–control studies had high refusal rates (>15%), potentially resulting in selection bias if drivers who refused participation had different rates of drug use than those who participated. Different methods to detect cannabis exposure in cases vs. controls (e.g., blood THC in cases and saliva THC in controls) were employed in many case-control studies, non-comparable controls (e.g., patients visiting hospital for medical problems) were recruited to estimate THC use in the general driving population (29), and only a fraction of included studies measured THC in blood samples or a combination of blood samples and urine or saliva samples or self-reports [Asbridge et al. 9 of 10 (2), Elvik 20 of 27 (7), Li et al. 2 of 9 (16), and Hostiuc et al. 10 of 24 studies (15)]. All of these limit the generalizability of findings.

In addition, whole blood, plasma, urine, and saliva are body fluids with different characteristics when it comes to assessment of THC levels. Experimental studies could not find a significant correlation between THC concentrations (logarithms) in oral fluid and plasma, while time influences THC concentrations in plasma and oral fluid differently after repeated oral THC doses (33). Cannabinoids in urine have a longer window of detection than blood and oral fluids, and THC's elimination is non-linear so that reverse extrapolation of concentrations to an earlier time is not feasible. When utilizing blood rather than plasma cannabinoid concentrations, concentrations must be approximately doubled because cannabinoids are tightly bound to proteins in plasma (>90%), and there is minimal partitioning into erythrocytes (34).

Also, cannabinoid blood and plasma concentrations were significantly higher in frequent smokers compared with occasional smokers at most time points for THC and 11-OH-THC (35). In oral fluids, THC levels above 2 μg/L were detected in occasional smokers for 26 h while frequent smokers had higher levels for >72 h. Thus, low THC concentrations can be detected for several days in oral fluids of chronic smokers similar to blood and urine (36). Eventually, the authors of the review comment that cannabinoid stability in these measures not only depend on characteristics of the body fluids used and the smoking status of the individuals, it also depends on collection method, buffer composition in commercial collection devices, the analytes, storage containers, and storage temperature and duration.

The third purpose of our analyses on the relationship between THC concentration and car crash risk was addressed by five case-control studies with "high quality (++)" SIGN rating (**Table 2**). None of the meta-analyses reported statistics on this relationship. However, the association is of importance since there are various legal cut-off values for THC blood levels across European countries for DUIC. While the penalty increases in Norway according to the THC concentration detected (1.3, 3, 9 ng/ml), other countries have cut-off values of 1 ng/ml (Germany, Belgium, Ireland, Luxemburg, Netherlands in the presence of other substances), 2 ng/ml (Czech Republic, United Kingdom), and 3 ng/ml (Netherlands) [EMCDDA Cannabis and Driving (5)]. It is a relevant issue whether studies report evidence using which of the legal cut-off concentrations supported by empirical data.

The Australian study (26) indicated a significantly higher risk for THC ≥ 5 ng/ml with the highest OR estimates across studies (OR 6.6) which is higher than ORs from later studies [Laumon et al. (27) unadjusted OR (uaOR) 4.7, Martin et al. (28) (uaOR) 3.95, and Brubacher et al. (29) (uaOR) 2.29 for the same subgroup of individuals with THC ≥ 5 ng/ml]. However, in the Drummer et al. sample, in 84% of the THC-only cases the THC concentration was ≥5 ng/ml and the median was 12 ng/ml. This rate is higher compared to the French and Canadian samples [Laumon et al. (27): 2.66%, Martin et al. (28): 4.2%, Brubacher et al. (29): 0.9%]. Therefore, based on the high rate of individuals with THC above 5 ng/ml, it was quite likely to see an effect of

THC on crash risk in the Australian sample. Further, in the Australian study (26), alcohol was commonly found in THC-positive cases (43%), the effect of THC was also evaluated in the THC plus alcohol cases and significant interaction was found. This interaction could not be replicated in French and Canadian samples. In the first French study (27), no statistical interaction between blood concentrations of THC and alcohol was detected as well as in the later studies (28, 29). Thus, most studies report a significant influence of cannabis and alcohol use on culpability for fatal crashes or injuries, but both substances obviously exert their effects independently (6). Results from the Australian Study (26) also suggested that both alcohol and cannabis showed a biological gradient with higher doses of both substances have a higher OR of culpability in fatal crashes. This significant dose-effect was also reported from the first French (27) and the Canadian Study (29), while in the second French study (28), the ORs show an inverse U-curve trend with a maximum at THC concentrations between >2 and <5 ng/ml, after controlling for alcohol intoxication. All authors across studies consistently argue that their studies yield a marked dose effect and a potential causal role of DUIC in fatal crashes. The latest study of Drummer et al. (30) confirmed the finding that elevated odds of culpability are positively associated with THC, particularly those with higher blood concentrations.

Culpability studies may be well suited to compare risk of fatal and non-fatal crashes, because THC blood levels were measured in all five samples. If THC blood levels are compared regarding fatal (26–28) and non-fatal crashes (29, 30), the odds ratios for any THC blood levels are similar [fatal crashes: 2.7 ng/ml (26), 1.78 ng/ml (27), 1.65 ng/ml (28) vs. non-fatal crashes 1.13 ng/ml (29), 1.9 ng/ml (30)] while the levels in fatal crashes tended to be higher. A previous meta-analysis and systematic review, which excluded low-quality studies, reported cannabis-associated risk for non-fatal crashes (OR = 1.74; 95% CI = 0.88–3.46) and for fatal crashes (OR = 2.1; 95% CI = 1.31–3.36) (2) and confirm the findings for the included five culpability studies in our analysis.

However, case-control and culpability studies have limitations. As several of the authors pointed out, estimating the degree of intoxication for cannabis is a more difficult task than for alcohol (26, 29). As far as cannabis is concerned, after smoking and vaporization, there is a delay in maximal cannabis effects compared to the peak THC blood concentration after consumption, with peak effects after ∼30 min depending upon study design and time of testing. Effects on cognition and psychomotor function do not decline as quickly as THC concentration decreases (37–40). When smoking a "joint," whole blood THC concentrations typically peak at >100 ng/ml during smoking and then drop so rapidly that THC is usually <2 ng/ml within 4 h of a single acute exposure (38). Psychotropic effects typically peak at 20–30 min and resolve by 4 h. Ingesting cannabis delays the onset and extends the duration of these effects. The main THC metabolite, 11-nor-9-carboxy-THC (THC-COOH), is not psychoactive and persists in blood and urine long after impairment resolves. Thus, THC-COOH provides evidence of previous cannabis exposure but does not necessarily indicate impairment or recent use (41). The active ingredient behind most of the effects of cannabis that impair driving ability is THC. Metabolites such as THC-COOH are present and detectable for a significant time after consumption but lack any proven psychoactive effects which impair driving ability.

The results of culpability and case-control studies must be compared with findings from experimental and laboratory studies. Laboratory and simulator studies certainly suffer from the limitation that they are conducted in an artificial environment. Thus, experimental data show that drivers attempt to compensate cannabis intoxication by slower driving after smoking cannabis, but their control deteriorates with increasing task complexity (5, 6). These behaviors limit the generalizability of experimental study results to authentic traffic situations (2). However, as with other cognitive tasks, cannabis smoking (THC-dominant and THC-CBD-equivalent) increases lane weaving after 40–100 min following vaporization (9) and impaired cognitive function consistently as well as critical-tracking tasks, reaction times, divided-attention tasks, and lane-position variability, all of which may increase car crash risk.

In general, however, there is no clear overall relationship with THC blood or serum levels and driving skills or crash risk from experimental studies, even if time of use and duration of consumption are considered. Not surprisingly, there is no unanimous agreement on potential THC legal cut-off levels despite the dose effect with higher THC blood concentrations resulting in higher OR estimates for crashes. However, a relationship does not necessarily provide a clue for a scientifically supported cut-off value. Experts suggest that many drivers with blood THC >3 ng/ml (42) or >3–5 ng/ml (43) have significant impairment and should be prohibited from driving. Based on these reports, many jurisdictions, including many US states and Canada, have set THC *per se* limits of 2 or 5 ng/ml, while many European countries have a limit of 1 ng/ml. Advocates of these lower THC concentrations argue that THC concentration drops rapidly after smoking, so a driver impaired with high THC concentrations at the time of driving could show concentrations below 5 ng/ml several hours later if there is a delay in obtaining blood samples (44), a fact that supports lower *per se* limits for THC (30). These concentrations, especially the 1 or 2 ng/ml levels, were criticized because they may not indicate impairment especially in frequent users who develop tolerance to some THC impairing effects (6, 42). Due to the accumulation of cannabinoids in fat, some daily users may have blood THC > 1 ng/ml after a week or more of abstinence (6). Therefore, the various THC concentrations used to define a cannabis-related driving offense in EU countries and some US-states varying between 1 and up to 7 ng/ml alone may not be appropriate to evaluate driving skill impairment comprehensively.

Measures of THC and its non-psychoactive metabolite THC-COOH within hours of an accident suffer from several limitations and may not reflect driving skill impairment. Even higher THC concentrations of >5 ng/ml in recent studies yielded higher risks of injuries and fatal concentrations, however not all studies reported statistically significant relationships. Rather, the assessment of both biological measures and psychomotor characteristics may render evaluation of driving fitness more accurate (more valid to "real" impairment) and is probably applicable in practical traffic control situations. Thus, future

experimental and laboratory research on cannabinoid's effects on fitness to drive should consider designs which include measures of psychomotor and cognitive functions like reaction times and decision making after long and monotonous drives and divided attention tasks. These cognitive characteristics may be most impaired by cannabis according to available research (5, 6).

Finally, it is important to recognize that an important compound of cannabis-products used is Cannabidiol (CBD). As for driving skills, it is a substance with sedative effects and therefore may play a role in impairing driving abilities and increase risks for accidents. However, no study investigates the influence of CBD alone on car crash risks. Certainly, since CBD is in increasing demand in sales and consumption, further studies are needed to evaluate the relationship between CBD use, driving ability, and car crash risks.

In summary, there is unanimous agreement across studies that acute cannabis use significantly increases the risk for car crashes and impairs specific driving skills, and confidence in the results from several types of studies (case-control, culpability, and cohorts) is rated "moderate" according to CERQual. In meta-analyses, cannabis user's ORs for car crashes are slightly but significantly increased, when several confounders are considered in multivariate analyses. Further, self-report vs. blood test, case control vs. culpability, and non-fatal crashes had higher OR estimates. High quality culpability studies (SIGN) noted that there is a dose effect of higher THC blood concentrations with increased risk for fatal crashes and those with injuries. However, this biological gradient does not provide a clear legal cut off value. Therefore, these cut off values still range between 1 and 5 ng/ml. While there are various problems related to the measure of THC and its metabolite THC-COOH in blood and other tissues within hours after a crash (different body fluids with different time frames of THC levels), these values may not even reflect actual driving skill impairment. Thus, the biological measures alone may be not appropriate to assess fitness to drive and should be combined with ratings of psychomotor and cognitive skills.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

UP, MH, DH, JW, and EH wrote, edited, and supervised the manuscript. MS, BL, and AH contributed on the CAPRIS study by conducting the literature search and evaluating it. All authors contributed to the article and approved the submitted version.

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Investigating the Residual Effects of Chronic Cannabis Use and Abstinence on Verbal and Visuospatial Learning

Valentina Lorenzetti[1]*, *Michael Takagi*[2], *Yvonne van Dalen*[3], *Murat Yücel*[4] and *Nadia Solowij*[5]

[1] Neuroscience of Addiction and Mental Health Program, Faculty of Health Sciences, Healthy Brain and Mind Research Centre, School of Behavioural and Health Sciences, Australian Catholic University, Melbourne, VIC, Australia, [2] Child Neuropsychology Unit, Murdoch Children's Research Institute, Melbourne, VIC, Australia, [3] Faculty of Science, University of Amsterdam, Amsterdam, Netherlands, [4] BrainPark, School of Psychological Sciences and Monash Biomedical Imaging Facility, The Turner Institute for Brain and Mental Health, Monash University, Melbourne, VIC, Australia, [5] School of Psychology and Illawarra Health and Medical Research Institute, University of Wollongong, Wollongong, NSW, Australia

Rationale: Regular cannabis users have been shown to differ from non-using controls in learning performance. It is unclear if these differences are specific to distinct domains of learning (verbal, visuospatial), exacerbate with extent of cannabis exposure and dissipate with sustained abstinence.

Objective: This study examines different domains of learning (verbal, visuospatial) in current and abstaining cannabis users, and the role of chronicity of use.

Methods: In a cross-sectional design, we examined 127 psychiatrically healthy participants (65 female) with mean aged of 34 years. Of these, 69 individuals were current regular cannabis users (mean 15 years use), 12 were former cannabis users abstinent for ∼2.5 yrs (after a mean of 16 years use), and 46 were non-cannabis using controls. Groups were compared on verbal learning performance assessed via the California Verbal Learning Test (CVLT-II) and for visuospatial learning measured with the Brown Location Test (BLT). We explored the association between CVLT/BLT performance and cannabis use levels in current and former users.

Results: Current cannabis use compared to non-use was associated with worse performance on select aspects of verbal learning (*Long Delay Cued Recall*) and of visuospatial learning (*Retroactive Interference* and *LD Rotated Recall*). Prolonged abstinence was associated with altered verbal learning but intact visuospatial learning. There were non-significant correlations between distinct cannabis use measures, age and learning in both current and former users.

Conclusions: Our findings suggest cannabis use status (current use, former use) affects different domains of learning (verbal and visuospatial) in a distinct fashion. These findings might be accounted for in the design of cognitive interventions aimed to support abstinence in cannabis users.

Keywords: cannabis (marijuana), verbal learning and memory, visuospatial learning, abstinence, tetrahydrocannabinol, California Verbal Learning Test—Second Edition, Brown learning test

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Aviv M. Weinstein,
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Delin Sun,
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***Correspondence:**
Valentina Lorenzetti
valentina.lorenzetti@gmail.com

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INTRODUCTION

Cannabis is the most widely used illicit substance globally (1) and its potency has doubled over the past decade (2, 3). These statistics are concerning as a substantial proportion of cannabis users consume it on a regular basis (4, 5) and a significant minority of people with regular use experience lower school attainment, depression, anxiety, psychosis, impulse-control disorders, suicidal ideation and addiction (6). While there is much to learn about the cognitive correlates of regular cannabis use, a growing body of research has produced increasing knowledge in this area.

One of the core features of regular cannabis use entails alteration of cognitive performance that last beyond acute intoxication, which is thought to reflect chronic residual effects of regular cannabis use (7–12). In particular, altered cognitive function in regular cannabis users affects the domains of learning and memory, which are critical for performing daily tasks, at school and at work (7–13). Therefore, learning and memory alterations in regular cannabis users may underscore lower academic attainment (14, 15) and occupational performance found in cannabis using samples (16, 17).

Poorer learning and memory performance have been documented in regular cannabis users in both verbal and visuospatial domains. Specifically, relative to controls, regular cannabis users have shown lower verbal learning and recall of words (7–12), lower recall and accuracy of visuospatial performance in a checkerboard test (18), and lower retrieval in the virtual Morris water maze task (19). There are some inconsistencies however, as some of the examined samples have not shown verbal/visuospatial learning and memory alterations, or alterations with small to moderate effect sizes (10–12, 18–22). Replication studies in larger samples are required to validate and further examine the association between cannabis use and learning/memory performance, particularly for the visuospatial domain which has been examined by few studies to date.

The role of the extent of cannabis exposure on verbal/visuospatial learning and memory alterations is unclear. Evidence suggests that higher chronicity of use predicts worse verbal learning and memory performance (23–29). However, there is a lack of empirical studies that tested in detail how distinct measures of cannabis exposure affect verbal/visuospatial learning. Such measures include: dosage, duration, age of use onset, hours from last use, potency (9, 10, 12, 30) and cannabinoids such as the main psychoactive compound Δ^9-tetrahydrocannabinol (THC) that determines cannabis potency (31–33). The lack of studies on how cannabis use patterns and THC levels affect learning performance in chronic users, creates a knowledge gap to inform users, educators, clinicians and policy makers about which measures and levels of cannabis exposure may be more harmful for verbal/visuospatial learning in chronic cannabis users.

Another issue yet to be elucidated is whether poorer verbal/visuospatial learning performance in regular cannabis users persists beyond prolonged abstinence, and the relevant evidence to date is mixed. Some studies show that learning deficits persist beyond abstinence [i.e., after 1 month (17, 30)]. Other studies found that learning alterations are attenuated (e.g., lower effect size) with longer abstinence (12) [e.g., over 4 to 8 weeks (34). Other studies show attenuated learning deficits in cannabis users who abstain for a variety of periods (11): 3 weeks (35), 1 month (36–40), 3 months (41)]; 12 months (35, 42–46). The inconsistency between study findings may be due to methodological confounds, such as long-lasting residual effects of chronic exposure e.g., cumulative lifetime exposure prior to quitting (30).

In sum, lower verbal learning performance has been (largely) consistently identified in chronic, long-term cannabis users. However, visuospatial learning deficits are largely unexplored, as well as the role of cannabis exposure levels and of prolonged abstinence.

The primary aim of this study was to address this evidence gap and to examine whether current cannabis use is associated with selective impairment of either verbal or visuospatial learning and memory. We also aimed to explore the role of extent of cannabis exposure and of prolonged abstinence on verbal/visuospatial learning and memory in chronic cannabis users.

To do this, we recruited 127 people (65 females), consisting of 69 current users and 12 former cannabis users and 46 non-using controls, comprehensively characterized for extent of substance use (alcohol, tobacco and other illicit drug use; cannabis use frequency, quantity, duration, age of onset, time from last cannabis use) and mental health (anxiety, depression and psychotic symptoms). Based on the existing evidence, we hypothesized that worse verbal and visuospatial learning performance would be apparent in cannabis users with more chronic levels of exposure.

MATERIALS AND METHODS

Participants

We recruited 127 people aged between 18 and 55 years via advertisements in local newspapers and Internet websites, and screened using a structured telephone interview to determine study eligibility. Participants included 69 current chronic regular cannabis users, 12 former chronic cannabis users and 46 non-using controls (henceforth called "current users," "former users," and "controls," respectively). All groups were age matched.

Inclusion and Exclusion Criteria

Cannabis users were included if they: (i) used cannabis at least twice a month for >2 years (the vast majority were currently using >3 days a week over many years, with a median of 30 smoking days/month and of 13 years of regular use); (ii) refrained from using substances other than cannabis, alcohol and tobacco in the month prior to assessment. Exclusion criteria for all participants were: (i) neurological disorders or serious head injury; (ii) Intelligence Quotient (IQ) <70; (iii) current regular use of illicit substances other than cannabis (amphetamines, benzodiazepines, cocaine, ecstasy, hallucinogens, inhalants and opiates; median lifetime use was between 0 and 6 occasions for any other drug).

All participants were requested to abstain from cannabis for at least 12 h prior to testing to enable examining cognitive

function in a non-intoxicated state, and provided written informed consent in accordance with local ethics committee guidelines. Ethics approval was given by the Mental Health Research and Ethics Committee (MHREC, I.D. number 459111), the Melbourne Health and North Western Mental Health (Melbourne, Australia), the Wollongong Human Research Ethics Committee (HREC, project number NSA07/03), and the ethics committee of the Murdoch Children's Research Institute (MCRI).

Procedure

Participants underwent a comprehensive 2.5 h long assessment of mental health, substance use and cognitive function.

Mental Health

We screened for psychiatric disorders through the Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders IV-R (47), and assessed global functioning via the Global Assessment of Functioning module of the DSM-IV (48). We examined psychopathology symptoms of anxiety (State and Trait Anxiety Inventory, STAI; (49), depression and psychosis (Community Assessment of Psychic Experiences, CAPE (50).

Substance Use

We assessed lifetime and past month substance use through semi-structured interviews, including the Substance Use History [Orygen Youth Health Research Centre, Melbourne, Australia (51–53)], a detailed structured assessment interview for cannabis (27), and the Timeline Follow-Back (54). From these interviews, we derived levels of tobacco use (cigarettes per week) and cannabis use (i.e., lifetime and past year cumulative dosages and frequencies of use, duration of use and age of onset).

We converted cannabis dosage to standardized units (i.e., cones, approximately equivalent to $\sim$ 0.1 g) (55). We measured urinary levels of the carboxy metabolite of THC (THC-COOH) via toxicology analysis, and THC accumulated in hair. Alcohol use (standard drinks per month) were quantified from the structured interviews and the Alcohol Use Disorders Identification Test (56).

Cognitive Function

We assessed *current IQ*, via the Wechsler Abbreviated Scale of Intelligence (WASI) (57) and *premorbid IQ* using the Wechsler Test of Adult Reading (WTAR) (58), respectively.

We measured *verbal learning and memory* via the California Verbal Learning Test, Second Edition (CVLT-II) (59), which was administered according to the manualized instructions. First, participants were asked to recall a list of 16 words presented orally (*List A*) for five consecutive trials (learning *Trials 1 to 5*). Then, participants were instructed to recall a new list of 16 words (*List B*). Subsequently, participants were asked to recall the words from *List A* without any cues to aid memory, and then with cues (*Short Delay Free Recall* and *Short Delay Cued Recall*). After a 20 min interval, the latter procedure was repeated (*Long Delay Free Recall* and *Long Delay Cued Recall*). Finally, participants were asked if they recognized, from among a list of 48 words including distractors, those words that were previously presented in *List A* (*Recognition Trial*).

Visuospatial learning was examined using the Brown Location Test [BLT (60)], a visuospatial analog of the CVLT-type verbal learning tasks. Participants were presented with 12 pages, one at a time, on which 58 identically sized black outlined circles were located. At each presentation, one of the circles was filled with a red dot and the location of the red dot was different on each page, thus forming a "list" of 12 red dot-locations to remember akin to the list of words to be remembered on each trial of a verbal learning task. After each trial (i.e., the serial presentation of the 12 pages), the participant was provided an identical page of circles where none were filled with red, and was asked to place red chips in the locations where the red dots had been presented. This procedure was repeated 5 times (learning *Trials 1 to 5*).

Then, participants were presented with a new series of 12 black dots, which they were also asked to recall as above (*Interference* trial). Subsequently, participants were asked to recall the locations of the red dots from *Trials 1–5* immediately after Interference (*Short Delay Recall*), after 20 min delay (*Long Delay Recall*), and after rotating the recall page 90 degrees. Finally, participants were presented with a page containing the original location of the red dots, and additional distractor red dots. Participants were asked to distinguish known 12 dot locations from 12 distractor dot locations (*Recognition* trial).

Statistical Analyses

Descriptive Demographic, Clinical, and Substance Use Data

As the majority of variables were skewed and not transformable, group comparisons for descriptive purposes were performed using chi-square tests for categorical variables (sex); as well as ANCOVAs for normally distributed discrete variables (IQ, STAI) and Kruskal-Wallis tests, followed by *post hoc* Mann-Whitney U tests, for non-normally distributed discrete variables.

Primary Aim

To examine group differences for CVLT and BLT performance, Quade's method (61) was used for not normally distributed data from the CVLT and the BLT. Quade's method enables running non-parametric tests comparing groups using covariates. With Quade's method, the dependent variable in ANOVA is the unstandardized residual of a linear regression between the ranked (in ascending order) dependent variable (CVLT and BLT scores) and the ranked covariates (IQ for CVLT, IQ, and age for BLT).

Comparisons between CVLT and BLT trials *within* groups were performed using Friedman- and *post-hoc* Wilcoxon signed rank tests.

Exploratory Correlations

Spearman's correlations were run to investigate how performance on the CVLT and BLT (residualized data after regressing out the effects of IQ on the CVLT data, and that of IQ and age on the BLT data) was associated with (i) THC or THC-COOH in hair and urine, respectively; and (ii) extent of cannabis use [duration, age at use onset, dosage (lifetime cumulative cones), frequency (smoking days/month), and hours since last cannabis use].

For all correlations, we utilized the conservative Bonferroni method to control for multiple tests and therefore readjusted the significance threshold to $\alpha = 0.0005$.

Covariates

We retained IQ as a covariate in all analyses of CVLT and BLT data. We used age as an additional covariate in BLT data analyses, as age was significantly associated with BLT measures in non-users. Sex was used as a within-groups factor in analyses of CVLT but not BLT performance, as it significantly affected the former but not the latter. Alcohol standard drinks/month, tobacco cigarettes/week and sub-diagnostic psychopathology symptoms (i.e., anxiety, depression, positive and negative psychotic symptoms) were not included as covariates because they did not significantly affect CVLT and BLT performance.

Sensitivity analyses

A series of two sensitivity analyses were performed to confirm the robustness of the effects. First, all analyses were repeated excluding 12 chronic users who used any illicit substances other than cannabis and these confirmed the results from the analyses run with the whole sample. Therefore, we report the results from the whole group analyses.

Second, we reran group comparisons without 7 current users who on the day of testing admitted to having used cannabis for less than the required at least 12 h—abstinence (range 3–10 h, median of 4 h). As these individuals did not show overt signs of acute intoxication, we proceeded with testing.

All analyses were conducted using SPSS, Version 21 (IBM).

RESULTS

Table 1 summarizes data on demographic, clinical and substance use measures for chronic users, former users and non-users.

Socio-Demographic and IQ Data

All groups were matched by age and premorbid IQ. Chronic users and controls had an equal composition of males and females. However, former users had a lower proportion of females to males, relative to both chronic users ($\chi^2 = 5.82$, $p = 0.016$, respectively) and non-users ($\chi^2 = 6.05$, $p = 0.014$).

Education years were lower in chronic users than non-users ($Z = -2.79$, $p = 0.005$), and IQ was also lower in chronic users than the other groups (i.e., controls [$t = -3.71$, $p < 0.001$], former users [$t = -2.42$, $p = 0.018$]). Global functioning was lower in both cannabis groups than controls (i.e., chronic users, $Z = -6.96$, $p = <0.001$; and former users, $Z = -3.80$, $p < 0.001$).

Alcohol and tobacco Use level

Alcohol use (standard drinks/month) was greater in former users compared to all groups (i.e., current users: $Z = -2.48$, $p = 0.013$, and controls: $Z = -2.83$, $p = 0.005$). Tobacco use (cigarettes/week) was greater in current users than former users, and lowest in controls ($Z = -2.13$, $p = 0.034$ and $Z = -3.24$, $p = 0.001$, respectively).

Cannabis Use level

The cannabis groups had similar cannabis use' duration, age of onset and lifetime dosage (see **Table 1**). However, current users smoked more days/week and consumed a greater amount of cannabis in the past year than former users.

Abstinence duration in current users was median of 16 h (range 3–336 h). Seven current cannabis users reported abstaining for 3 to 10 h despite our request to abstain for at least 12 h; and therefore analyses were repeated excluding these very recent users. Abstinence duration in former users was a mean of 2.5 years (median 6 months, range 1 month−19 years); 9 former users had ceased cannabis use within the past 12 months.

Subclinical Psychopathology Symptoms

Symptom severity for anxiety, depression and psychosis was greater in current users than controls ($t = 4.11$, $p < 0.001$; $Z = -4.04$, $p = <0.001$; $Z = -2.66$, $p = 0.008$; $Z = -3.41$, $p = 0.001$, respectively), but did not differ between the other groups (p = n.s.).

Group Differences in CVLT Performance

Table 1 Overviews group differences in CVLT performance. Group differences in CVLT trials are overviewed below, followed by learning curves and learning trials in each of the three groups (controls, current users, former users).

CVLT Trials

Group differences emerged for 7 out of the 18 CVLT variables: *Trials 1, 3, 1–5, B, Short Delay Free Recall, Long Delay Free Recall* and *Long Delay Cued Recall* (see **Table 2**).

Current Users vs. Controls

Cannabis users performed worse than controls for CVLT *Trial 1* ($F = 6.52$, $p = 0.012$), and learning from *Sum Trials 1–5* ($F = 4.54$, $p = 0.035$). Additionally, current users recalled less words than controls for CVLT *List B* ($F = 10.08$, $p = 0.002$), *Short Delay Free Recall* ($F = 4.37$, $p = 0.039$) and *Long Delay Free Recall* ($F = 5.12$, $p = 0.026$). These group differences did not survive a sensitivity analyses that we ran after excluding seven current users who consumed cannabis recently <12 h before testing.

After running the sensitivity analysis, the only performance difference that emerged in cannabis users vs. controls was poorer performance by users in *Long Delay Cued Recall* ($F = 4.35$, $p = 0.015$).

Former Users vs. Controls

Similarly to current users, former users vs. controls showed lower CVLT performance for *Long Delay Cued Recall* ($F = 4.42$, $p = 0.040$), *Trial 1* ($F = 6.95$, $p = 0.011$), and learning from *Sum Trials 1–5* ($F = 5.14$, $p = 0.027$). Additionally, former users performed worse than controls on *Trial 3* ($F = 6.04$, $p = 0.017$).

CVLT Learning Curves

As shown in **Figure 1**, CVLT learning curves improved for all groups at every trial from *Trial 1* to *Trial 4* (all $p < 0.001$). Controls improved word recall at every trial from *Trial 1* to *Trial* (Z range from −5.71 to −4.54, $p < 0.001$). Similarly to controls, current users improved word recall at *every trial from Trial 1 to*

TABLE 1 | Socio-demographic, cannabis and other substance use, and psychopathology symptoms current and former chronic cannabis users and controls.

		Controls	Cannabis users	Former cannabis users	Z	*p*	df
Socio-demographic, IQ, alcohol/tobacco							
Total *N* [female]†‡		46 (26)	69 (37)	12 (2)	$\chi^2$6.53	0.038	2
Age, yrs		31.17 (12.83)	32.68 (11.17)	37.83 (11.03)	3.34	0.188	126
Education, yrs*		13.97 (1.60)	12.82 (2.25)	13.17 (2.41)	7.90	0.019	122
Premorbid IQ		106.78 (10.18)	101.40 (13.29)	106.75 (5.01)	5.55	0.062	125
IQ*‡		111.76 (10.91)	104.15 (10.72)	112.25 (11.21)	7.22	0.001	125
Global functioning*†		85.5 (4.95)	73.7 (9.77)	75.58 (9.64)	50.32	<0.001	126
Alcohol use (drinks/mo)†‡		18.49 (23.89)	24.52 (32.74)	52.48 (32.80)	9.43	0.009	126
Tobacco (cigarettes/week)*†‡		4.95 (16.79)	58.95 (53.15)	29.33 (38.16)	56.56	<0.001	126
Cannabis use							
Frequency, days/mo	Lifetime‡	NA	23.24 (6.89)	28.83 (4.04)	−3.63	<0.001	80
	Past 12 mo‡	NA	24.59 (8.62)	3.33 (8.51)	−4.81	<0.001	80
Dosage, cones	Lifetime	NA	69,183 (73,271)	43,036 (36,492)	−1.17	0.241	80
	Past 12 mo‡	NA	5,070 (4039)	136.3 (375.3)	−5.30	<0.001	80
Duration of regular use, yrs		NA	15.13 (10.00)	15.92 (9.61)	−0.297	0.767	80
Onset age, yrs		NA	16.96 (3.93)	17.33 (3.75)	−0.510	0.610	80
Abstinence duration, yrs		NA	NA	2.46 (5.56)	NA	NA	12
Psychopathology symptom scores							
Trait anxiety, STAI		33.64 (7.39)	41.99 (12.19)	35.33 (13.39)	2.13	0.12	124
Depression, CAPE*		12.29 (2.69)	15.06 (3.87)	13.58 (2.75)	16.34	<0.001	125
Positive psychotic, CAPE*		24.56 (3.37)	27.58 (6.21)	25.82 (3.22)	7.46	0.024	121
Negative psychotic, CAPE*		22.26 (5.11)	26.51 (6.95)	23.42 (13.39)	11.95	0.003	122

*NA, not applicable; *Significant difference between cannabis users and controls. †Significant difference between former cannabis users and controls. ‡Significant difference between cannabis users and former cannabis users. χ^2, for results from Kruskal-Wallis test; Z for results from Mann-Whitney U test; F values for IQ and anxiety. Current and premorbid IQ measured with the Wechsler Abbreviated Scale of Intelligence and the Wechsler Test of Adult Reading, respectively; Alcohol use measured with the Alcohol Use Disorders Identification Test; Anxiety symptoms measured with the State and Trait Anxiety Inventory (STAI), depression, positive and negative symptoms measured with the subscales of the Community Assessment of Psychic Experiences (CAPE); Global functioning measured with the module of the DSM-IV.*

Trial (Z range from −6.83 to −2.58, $p < 0.01$). Former users only significantly improved their word recall from *Trial 1* to *Trial 2* ($Z = -3.08$, $p = 0.002$).

CVLT Delayed Recall

Controls

Controls showed a significant increase in the ***Long*** *Delay* ***Free*** *Recall vs.* ***Short*** *Delay Free Recall* ($Z = -3.09$, $p = 0.002$) and ***Long*** *Delay* ***Cued*** *Recall vs.* ***Short*** *Delay Cued Recall* ($Z = -3.25$, $p = 0.001$).

Additionally, controls improved significantly only after cues were given, in the *Short Delay Cued Recall* trial ($Z = -2.14$, $p = 0.032$).

Current Users

Similarly to controls, current users showed a significant increase in the ***Free Long*** *Delay Recall* vs. ***Free Short*** *Delay Recall* ($Z = -2.79$, $p < 0.005$) and ***Cued Long*** *Delay Recall vs.* ***Cued Short*** *Delay Recall* ($Z = -2.28$, $p = 0.023$). In contrast to controls, current users performed better during *Cued Recall vs. Free Recall* for the *Short Delay* trial ($Z = -3.06$, $p = 0.002$) and for the *Long Delay* trial ($Z = -2.12$, $p = 0.034$).

Former Users

Former users did not show differences in any delayed recall trials.

Exploratory Correlations Between CVLT Performance, Cannabis Use Measures, and Age

Older age was not associated with any CVLT variables in cannabis users, but was associated with better recall at *Trial 5* ($rs = 0.465$, $p = 0.001$) and more *Intrusions* in controls ($rs = 0.291$, $p = 0.045$) and with greater *Recognition of False Positives* in former users ($rs = 0.602$, $p = 0.029$).

Current Users

Greater cannabis frequency over the lifetime was associated with lower *Retroactive Interference* and greater *Loss After Consolidation*; and greater frequency of cannabis use in the past year was associated with worse recall at *Trial 1*. More cumulative cannabis dosage in the lifetime was correlated with worse recall at *Trial 1* and worse *Retroactive Interference*; and greater past year cumulative dosage was correlated with worse recall at *Trial 1*. Earlier age of onset was correlated with less *Intrusions,* lower *Retroactive Interference* and greater *Proactive Interference.*

Former Users

In former users, greater frequency of cannabis use in the past year was associated with greater recall at *Trial 1*, greater *Recognition of False Positives* and lower *Intrusions*. Greater past year cumulative

TABLE 2 | CVLT-II performance in *current* users, *former* users, and controls: mean (standard deviation).

CVLT trials	Controls	Current users	Former users	F-value	*p*	df
Trial 1*†	8.30 (2.05)	6.96 (2.29)	6.62 (2.14)	5.09	**0.01**	127
Trial 2	11.39 (2.33)	10.30 (2.65)	9.92 (2.14)	1.53	0.22	127
Trial 3†	13.07 (1.93)	11.77 (2.66)	11.00 (2.68)	3.67	**0.03**	127
Trial 4	13.59 (2.04)	12.35 (2.51)	12.15 (2.94)	1.95	0.15	127
Trial 5	13.91 (1.87)	13.00 (2.51)	12.69 (2.69)	0.91	0.41	127
Trials 1–5*†	60.26 (7.98)	54.38 (10.92)	52.38 (10.56)	3.85	**0.02**	127
List B*	7.07 (2.02)	5.59 (2.18)	6.00 (2.16)	5.40	**0.01**	127
Short delay free recall*	12.98 (2.24)	11.42 (2.87)	11.38 (2.99)	2.74	**0.07**	127
Short delay cued recall	13.46 (2.00)	11.96 (3.07)	12.00 (2.77)	2.10	0.13	127
Long delay free recall*	13.65 (2.07)	11.91 (3.11)	11.77 (2.98)	3.65	**0.03**	127
Long delay cued recall†	13.87 (1.89)	12.28 (2.95)	11.77 (3.11)	3.35	**0.04**	127
Recognition	15.28 (0.958)	14.67 (1.50)	15.38 (0.961)	2.14	0.12	127
Recognition false positives	0.91 (1.75)	1.67 (2.42)	1.92 (2.96)	0.62	0.54	127
Repetitions	4.30 (3.81)	4.49 (4.06)	4.46 (5.24)	0.02	0.98	127
Intrusions	2.07 (2.99)	2.22 (2.92)	3.77 (5.31)	0.10	0.91	127
Proactive interference	1.24 (2.43)	1.36 (2.14)	0.62 (1.50)	1.09	0.34	127
Retroactive interference	0.94 (1.78)	1.58 (1.81)	1.31 (1.75)	1.03	0.36	127
Loss after consolidation	0.26 (1.73)	1.09 (1.88)	0.92 (11.71)	1.50	0.23	127

**Significant difference between cannabis users and controls. †Significant difference between former cannabis users and controls. CVLT-II, California Verbal Learning Test Version 2. Proactive Interference, prior learning interfering with new learning (Trial 1- List B); Retroactive Interference, later learning interfering with previous learning (Trial 5—Short Delay Free Recall) and Loss after Consolidation, loss of recalled words after delay (Trial 5—Long Delay Free Recall).*

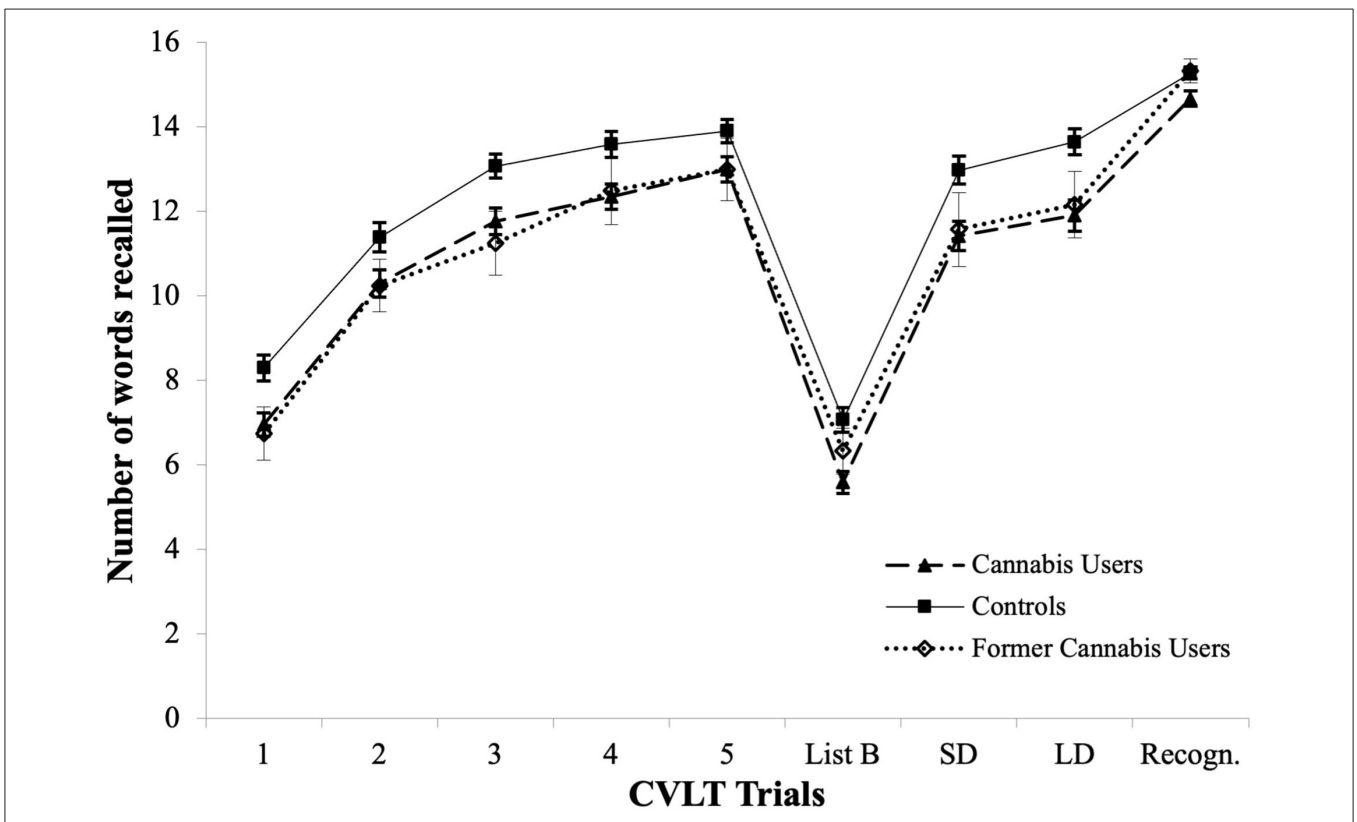

FIGURE 1 | CVLT learning curves across Trials 1–5, in current cannabis users, former cannabis users and controls, and mean performance for List B, Short Delay Free Recall (SD), Long Delay Free Recall (LD), and Recognition Trial (Recogn.).

dosage was correlated with worse recall at *Trial 4*. Earlier age of onset was correlated with better recall at *Trials 1, 2, 3, 4, 1–5,* and *Trial B*.

None of the correlations run between CVLT performance and cannabis use levels in current and former users survived Bonferroni correction for multiple tests (see **Supplementary Tables 1, 2**).

Group Differences in BLT Performance

BLT trials

One cannabis user did not complete the BLT, hence for these analyses $n = 68$ current cannabis users. BLT performance differed between groups for 2 of the 15 variables (see **Table 3**). Current users performed significantly worse than controls on *Retroactive Interference* and on *Long Delay Rotated Recall* ($F = 5.95$, $p = 0.016$ and $F = 1.62$, $p = 0.014$). Current users performed worse than former users on *Short Delay Free Recall* ($F = 4.28$, $p = 0.042$).

Sensitivity analyses for BLT trials

After exclusion of seven participants who reported using cannabis within 12 h of the assessment, impaired performance persisted in current users vs. controls, for both *Retroactive Interference* ($F = 3.29$, $p = 0.041$) and *Long Delay Rotated Recall* ($F = 3.13$, $p = 0.048$).

BLT learning curves

BLT learning curves are shown in **Figure 2**. The pattern of results was identical to that of the CVLT: current users, former users and controls showed significant improvement in recall [$\chi^2_{(4,68)} = 109.0$, $p < 0.001$; $\chi^2_{(4,12)} = 24.89$, $p < 0.001$ and $\chi^2_{(4,46)} = 114.7$, $p < 0.001$ respectively]. Current users and controls improved at every trial from *Trial 1 to Trial 4* (Z range between −4.38 and −2.01, $p < 0.04$; and Z range between −4.88 and −3.52, $p < 0.001$, respectively). Former cannabis users only improved between *Trial 1* and *Trial 2* (see learning curves in **Figure 2**, $Z = -2.57$, $p = 0.010$).

BLT Delayed Recall

Current users showed worse BLT performance in *Delayed Recall* only after *Page Rotation* ($Z = -4.76$, $p < 0.001$). None of the groups showed a difference between *Short Delay Recall* and *Long Delay Recall*.

Exploratory correlations Between BLT Performance, Age, and Cannabis Use Measures

There was no association between age and BLT performance in neither current users, former users and controls.

Current users

In current cannabis users, greater lifetime cannabis use frequency was correlated with lower BLT recall at *Trial 1–5 Total*, and greater *Recognition of False Positives*. Greater THC-COOH in urine was associated with lower performance during *Interference* and better performance during the *Proactive Interference* trial.

Former users

In former cannabis users, greater frequency of cannabis use in the lifetime was associated with greater recall at BLT *Trial 3, Trial 4, Trial 1–5 Total, Long Delay Free Recall, Long Delay Rotated Recall* and greater *Recognition Hits*. Later age of cannabis use onset was associated with lower recall at *Trial 3* and *Trial 4,* and lower *Recognition Hits*. Greater abstinence duration was associated with greater *Long Delay Free Recall* and *Long Delay Rotated Recall*.

None of the correlations between BLT performance, cannabis use levels and age in any groups survived Bonferroni correction for multiple tests (**Supplementary Tables 3, 4**).

DISCUSSION

This study shows that cannabis use status (current vs. former use) and extent of cannabinoid exposure have a differential impact on specific measures of verbal and visuospatial learning. Specifically, select measures of verbal learning in current and former cannabis users were impaired i.e., *Long Delay Cued Recall* of the CVLT. Instead, visuospatial learning was impaired only in current users i.e., *Retroactive Interference* and *Long Delay Rotated Recall* of the BLT. Performance on the CVLT and BLT was not significantly associated with any measures of cannabis exposure.

Poorer CVLT *Long Delay Cued Recall* performance in current cannabis users was robust to sensitivity analyses which excluded 7 people who did not appear intoxicated but admitted having smoked cannabis recently i.e., <12 h before testing (instead of the required >12 h), and persisted in former users. Therefore, lower *Long Delay Cued Recall* may reflect the residual effects of chronic cannabis use that are long-lasting and detectable well-beyond prolonged abstinence. This interpretation is consistent with findings that verbal learning alterations in cannabis users are apparent after THC metabolites are no longer detected in urine (9), and in cannabis users with chronic exposure reflected by long duration [i.e., 16 yrs (25) and 23 yrs (24)], dependent and almost daily use (62).

However, these notions are not supported by the lack of robust correlations between *Long Delay Cued Recall* and any measure of cannabis exposure including abstinence durations and chronicity of use. Therefore, the specific indices of cannabis exposure driving CVLT alterations in these groups of current and former users are unclear. Of note, verbal learning is ascribed by the function of posterior and frontoparietal cortices (41, 46, 63–65) that are high in cannabinoid receptors and thus might be vulnerable to the long lasting effects of repeated impact of cannabinoid exposure via complex neural mechanisms (66).

Surprisingly, most of the CVLT performance differences between current users and controls (i.e., *Trial 1, Sum Trials 1–5, List B, Short Delay Free Recall, Long Delay Free Recall*) were no longer detectable after sensitivity analyses without 7 people who recently smoked cannabis i.e., <12 h before testing. Therefore, recent cannabis exposure may drive alterations of select components of verbal learning alterations (17, 24, 27, 41, 46, 62). This notion is supported by other study findings that better Ray Auditory Verbal Learning Test performance is associated with longer abstinence duration (67) (*List B*

TABLE 3 | BLT performance in *current* cannabis users, *former* cannabis users and *controls*: mean (standard deviation).

BLT trials	Controls	Current users	Former users	F	*p*	df
Trial 1	3.93 (2.03)	3.93 (2.01)	3.54 (1.56)	0.05	0.95	126
Trial 2	5.85 (2.38)	5.24 (2.10)	5.85 (1.95)	0.47	0.62	126
Trial 3	7.00 (2.69)	6.22 (2.44)	6.46 (2.79)	0.54	0.58	126
Trial 4	8.72 (2.66)	7.26 (2.69)	7.85 (3.39)	1.80	0.17	126
Trial 5	8.72 (2.86)	7.78 (2.92)	8.77 (2.92)	0.82	0.45	126
Trials 1–5	34.22 (10.84)	10.43 (9.90)	32.46 (9.17)	0.73	0.49	126
Interference	3.72 (2.04)	3.19 (1.72)	3.23 (1.42)	0.04	0.96	126
Short delay free recall‡	7.93 (2.93)	6.22 (2.92)	8.15 (3.13)	3.74	**0.03**	126
Long delay free recall	7.76 (2.81)	6.50 (2.87)	7.23 (3.68)	1.40	0.25	126
Long delay rotated recall*	7.15 (3.18)	5.34 (2.87)	6.69 (3.43)	2.53	**0.08**	126
Recognition	18.70 (3.41)	16.78 (3.46)	17.69 (4.68)	1.80	0.17	126
Recognition false positives	3.00 (2.29)	3.99 (2.28)	3.00 (2.31)	1.60	0.21	126
Proactive interference	0.22 (2.30)	0.74 (2.35)	0.31 (2.53)	0.19	0.83	126
Retroactive interference*	0.78 (1.53)	1.56 (2.10)	0.62 (1.56)	3.51	**0.03**	126
Loss after consolidation	0.96 (1.66)	1.28 (1.91)	1.54 (1.51)	1.15	0.32	126

**Significant difference between cannabis users and controls. ‡Significant difference between cannabis users and former cannabis users. Proactive Interference, prior learning interfering with new learning (Trial 1—List B); Retroactive Interference, later learning interfering with previous learning (Trial 5—Short Delay Free Recall) and Loss after Consolidation, loss of recalled words after delay (Trial 5—Long Delay Free Recall).*

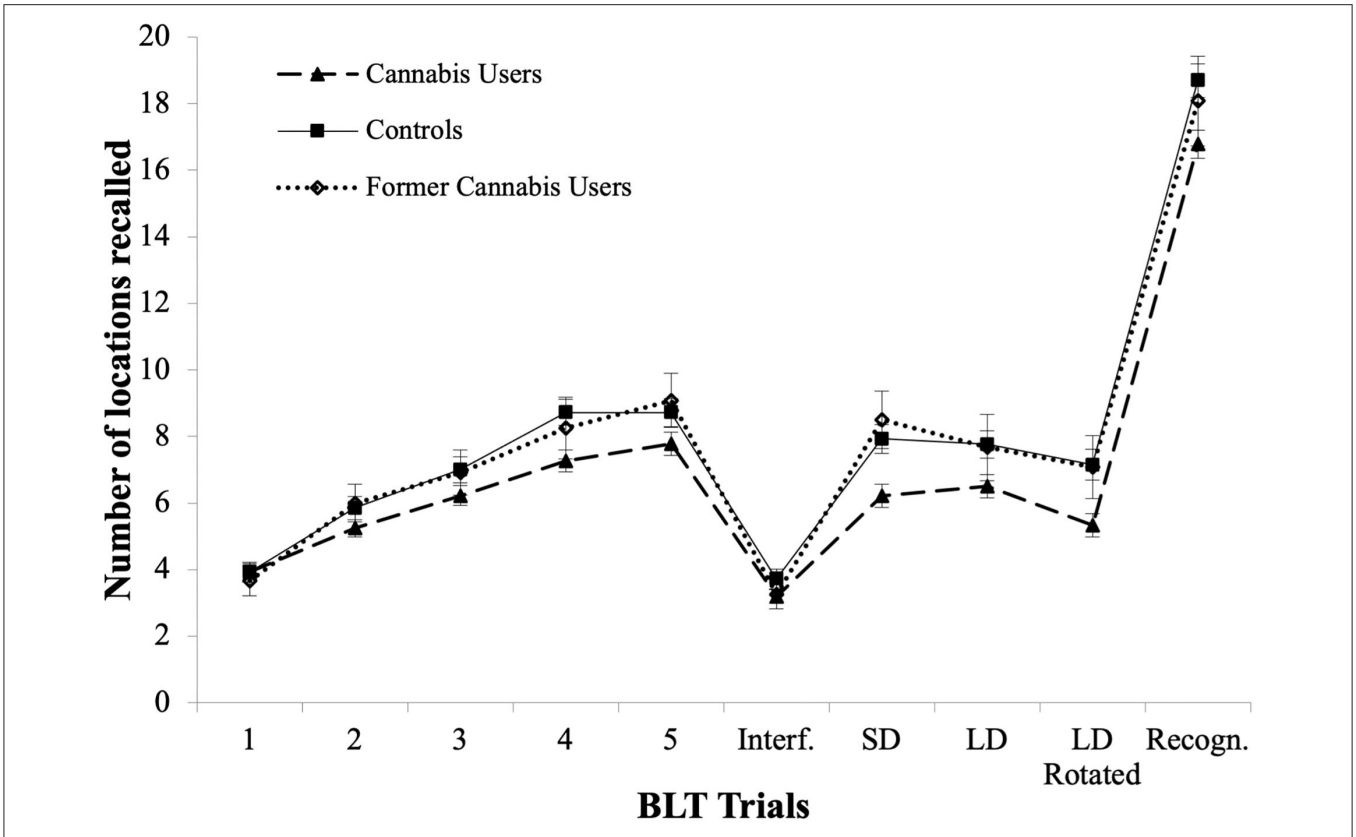

FIGURE 2 | BLT learning curves for Trials 1–5, in current users, former cannabis users and controls, as well as for Interference Trial (Interf.), Short Delay Free Recall (SD), Long Delay Free Recall (LD), Rotated Long Delay Recall (Rotated), and Recognition Trial (Recogn.).

(27), *total words recalled* (12, 24). However, we found no significant correlation between better CVLT performance and number of hours from last cannabis use or urinary THC metabolites. Thus, the strength of this finding needs to be verified in future studies that carefully measure abstinence duration (68), as only a few studies of verbal learning to

date report how long people abstained from cannabis before testing (25, 35).

Poorer visuospatial learning performance in cannabis users emerged in select BLT measures (*Retroactive Interference* and *Long Delay Rotated Recall*). These differences were robust and survived sensitivity analyses without a subgroup of recent users. Our findings are consistent with reports that visuospatial learning alterations in cannabis users affect *recall* but not *acquisition* trials (19, 45), but contrast previous meta-analytic findings that failed to find group differences (12).

The discrepancy between our results and those from previous work, might be due to systematic differences between sample characteristics and the tools used to assess visuospatial learning. First, our sample was older (i.e., ∼34 years) than the meta-analyzed samples i.e., <26 yrs (12). Interestingly, previous evidence shows that aging affects visuospatial learning (69–71). Therefore, lower visuospatial *recall* may be due to altered aging processes in cannabis users. However, the lack of significant correlations between age and BLT performance in this study does not support this notion and is to be further tested in future work. Second, the meta-analyzed studies to date used measures of visuospatial learning other than the BLT. Such measures (e.g., accuracy and total scores from the Rey-Osterrieth and Bender Visual-Motor Gestalt Test) might not have been sensitive enough to detect alterations specific to *recall* rather than *acquisition* trials (12).

The mechanisms underlying altered BLT in *recall* trials in current users are unclear. One candidate mechanism is impaired executive functioning (45, 72–74). Indeed, recall—but not acquisition—relies on executive function (75). Also, aging significantly affects the integrity of para-hippocampal and cingulate cortices that are concurrently ascribed to visuospatial learning, and to the residual effects of regular cannabis exposure (19).

Interestingly, we found for the first time that both current and former users showed similar *Learning Curves* across the verbal and visuospatial domains, suggesting the employment of common learning strategies across both domains (73). This similarity was apparent, given the similar structure of the BLT and the CVLT (i.e., both tests start with 5 *Learning Trials*, followed by an *Interference* trial and *Delayed Recall* trials). The overlapping *learning curves* between current and former users (see **Figure 1**), suggest that alteration of *learning curves* commences during regular use and does not recover after prolonged abstinence.

There are several limitations to this study. First, we examined a small sample of former users, and our findings require validation in larger samples. Second, our group of current users were *not* matched to controls for level of education, IQ and severity of sub-clinical psychopathology symptoms. Nevertheless, premorbid IQ was matched between groups, and we controlled for current IQ i.e., by using IQ as a covariate in all group comparisons (years of education were not associated with any performance measures and were thus not included as a covariate).

We also minimized potential confounding impact of severe mental health conditions on cognitive performance, by screening for any diagnoses of psychopathology. However, we cannot rule out that sub-clinical psychopathology symptoms in our sample, which are shown to exacerbate cognitive deficits (15), may have driven our findings on cognitive alterations. Since sub-clinical psychopathology symptoms as measured in this study did not exert a significant effect on performance, they were therefore not included as covariates in the analyses. On the other hand, our sample is representative of cannabis users within the general community, where higher (although not diagnosable) psychopathology symptoms and worse cognitive outcomes have been consistently reported (14, 76–79).

Third, correlational analyses were run in current users and former users including males and females, and not in different sexes separately, therefore precluding a detailed understanding of possible sex differences in the emerging alterations. Our strategy mitigated type-1 errors, as we have run a substantial number of correlational analyses in current and former cannabis users across all cognitive variables examined. Fourth, the number of abstinent users ($n = 12$) was small for statistical analyses, and findings pertaining to this group require replication in larger samples. Further, the cross-sectional study design and the lack of information on the sample' resilience levels, prevented to determine if abstinence was the reason for better performance compared to current usage, or the consequence of a latent factor such as resilience that also leads to better performance.

Our findings might be accounted for in the design of cognitive interventions aimed to support abstinence in cannabis users. For example, if a clinical practitioner knew that a patient uses cannabis regularly, and that regular cannabis use is associated with impaired *Long Delay Cued Recall*, the practitioner may implement strategies to ensure that their client recalls information/instructions critical for engaging with the treatment (e.g., repeating or asking the client to repeat the instruction/information, sharing written instructions). Also, knowing that regular cannabis users have worse performance on *Retroactive Interference and LD Rotate Recall,* could indicate to a practitioner that visuospatial information relevant for the treatment (e.g., the location of appointment/testing/treatment sites) may not be retained when learning occurs; and may prompt the practitioner to implement strategies to boost recall of visuospatial information relevant for the patient to attend treatment (e.g., sharing a map or sending a text reminder with information on appointment/testing/treatment sites).

In conclusion, our findings suggest that current cannabis use is associated with chronic residual effects on select aspects of verbal learning (*Long Delay Cued Recall*) and of visuospatial learning (*Retroactive Interference* and *Long Delay Rotated Recall*). Prolonged abstinence in former users was associated with altered verbal learning but intact visuospatial learning, suggesting that abstinence has a different impact on distinct domains of learning. Our findings warrant the conduct of future work that systematically tracks how learning performance in chronic cannabis users is affected during intoxication to map acute-on-chronic effects, residual effects beyond intoxication, and those that remain with prolonged abstinence, to track how the residual-on-chronic effects dissipate over time. Additional studies with careful assessment of cannabis use indices and exposure to THC and other cannabinoids, should examine how these findings

extend to cannabis user groups who experience worse mental health outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethics approval was given by the Mental Health Research and Ethics Committee (MHREC, I.D. number 459111), the Melbourne Health and North Western Mental Health (Melbourne, Australia), the Wollongong Human Research Ethics Committee (HREC, project number NSA07/03), and the ethics committee of the Murdoch Children's Research Institute (MCRI). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MT and VL drove data collection. VL drafted and revised the manuscript writing and statistical analyses and interpretation. YD contributed to the drafting and the running of the statistical analyses. MY and NS drove the study design. All authors revised the manuscript and contributed to the interpretation of the findings.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.663701/full#supplementary-material

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From Enchantment to Disillusion: A Narrative Exploration of Cannabis Use Disorder Among Young Israeli Combat Veterans

Miri Serebro[1], *Shira Sobol-Goldberg*[2] *and Daniel Feingold*[3]*

[1] MA Program, Psychology Department, Ariel University, Ariel, Israel, [2] School of Social Work, Bar-Ilan University, Ramat Gan, Israel, [3] Psychology Department, Ariel University, Ariel, Israel

Introduction: Substance use is common among military personnel and war veterans, especially combat veterans. Despite substantially high prevalence of cannabis use and Cannabis Use Disorder (CUD) consistently reported among veterans, little is known about psychological factors which may underlie CUD among this population.

Methods: In this study, we used narrative analysis in order to interpret retrospective in-depth interviews of combat veterans ($N = 12$) who were released from mandatory military duty during the past 5 years and currently qualified for a diagnosis of CUD. Participants were recruited from a larger quantitative study were eligible for participation if they screened positive for a diagnosis of CUD according to the Cannabis Use Disorder Identification Test- Revised (CUDIT-R) questionnaire. CUD diagnosis was validated in-person using the cannabis section of the Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 (AUDADIS-5) interview protocol. All interviews were transcribed and coded using the content analysis procedure.

Findings: Five main themes were extracted: (a) Traumatic events (b) Attitudes toward cannabis use (c) Combatant identity (d) The role of authority/father figures, and (e) Moral crisis. A meta-theme has been identified, "from enchantment to disillusion," representing a gradual psychological shift from a hopeful, highly motivated stance into the current state of mental rupture and moral injury, which are unsuccessfully compensated by excessive use of cannabis.

Conclusions: This study shed light on the etiology of CUD among young combat veterans, highlighting the role of supposed self-medication for trauma and sense of betrayal.

Keywords: cannabis, disorder, Israeli, veterans, disillusion, trauma

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Alessio Simonetti,
Baylor College of Medicine, United States
Georgios Demetrios Kotzalidis,
Sapienza University of Rome, Italy

***Correspondence:**
Daniel Feingold
d.y.feingold@gmail.com

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INTRODUCTION

Cannabis is the most commonly used drug, globally, with an estimated 192 million people, equivalent to 3.9% of the world population, who used cannabis during 2019 (1). In the past decades accumulating evidence has emerged associating cannabis use with several adverse long-term effects, particularly among individuals who use high-potency cannabis and those who use it frequently

(2). One such risk is developing Cannabis Use Disorder (CUD), a clinical condition associated with cannabis use which lasts at least 12 months, characterized by physical and psychological dependence as well as functional impairment caused directly by the use of cannabis. A 2.5% past-year prevalence of a CUD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5; (3)] has been reported in the U.S (4), with ∼27% of lifetime cannabis users developing CUD (5).

Several factors have been associated with increased risk for transition to CUD. For example, higher frequency and quantity of cannabis use (6), co-occurring psychiatric disorders, early initiation of cannabis use and childhood traumatic events (5). Military veterans have been identified as a population highly inclined toward cannabis use and CUD. Following nicotine and alcohol, cannabis is the most commonly used addictive substance among veterans (7), who commonly initiate cannabis use following their release from duty due to its legal status (8). Approximately 70% of veterans who initiate cannabis use will become regular users, and more than 20% will develop a DSM-IV diagnosis of cannabis abuse or dependence (9). It has been reported that between 2002 and 2009, prevalence of cannabis dependence has nearly doubled among U.S. veterans (10).

It has been suggested that combat veterans are specifically more prone to cannabis use and CUD compared to non-combat veterans (11). This may be attributed to various factors, including high rates of chronic pain among combat veterans (12). Furthermore, combat exposure has been associated with increased risk for frequent cannabis use (13), presumably due to the mediating role of post-traumatic stress symptoms and Post-traumatic Stress Disorder (PTSD), which has been extensively studied as a risk factor for developing CUD among veterans. Notably, as other factor may also underlie combat veterans' proneness to CUD, the use additional research methodologies has been recently encouraged (12). For example, growing attention is drawn to the effect of moral injury, a shame and guilt-based trauma-related syndrome which may develop among veterans, and its effect on various future outcomes (14, 15). However, yet little is known concerning its contribution to CUD (13), nevertheless in qualitative studies.

'To the best of our knowledge, little is known concerning combat veterans' narratives regarding cannabis use and CUD. In a recent study, Krediet et al. (16) interviewed a focus group comprised of Dutch veterans for whom cannabis was prescribed for medical purposes. Participants emphasized using cannabis for the purpose of attenuating their post-traumatic symptoms, primarily sleep disturbances, and were reluctant to report using cannabis for additional purposes. However, this study focused on medical marijuana users and could not be generalized to recreational cannabis use and CUD (17).

In Israel, rates of cannabis use within the general population were traditionally lower compared to the U.S. and Europe (18). However, by 2016, rates of cannabis use have increased substantially from ∼9 to 27% for past-year prevalence (19). In a recent investigation among Israeli combat veterans, more than 50% reported using cannabis in the past year (13). Military service in Israel is mandatory, lasting for 30 or 36 months for women and men, respectively. Israeli combatants have historically enrolled in two primary duties. The first is conventional warfare surrounding the country's borders, including traditional combat-related experiences such as being attacked or ambushed (20). The second includes policing and confrontation with the Palestinian civilian population in heavily-populated urban environments (21).

In this study, we sought to explore narratives of Israeli combat veterans recently released from military duty, and who currently qualified for a CUD diagnosis. In particular, we aimed to explore the extent to which major life events prior to, during and following military service emerge as correlates of transition to CUD. An a-priori hypothesis (22) was that lifelong traumatic events, including life-threatening events associated with PTSD (12) as well as morally conflicting events which are common in battle (13), will emerge as themes among combat veterans with CUD.

METHODS

Participants

Participants were 14 individuals who were recruited from a larger quantitative study focusing on veterans recently released from combat duty who had used cannabis regularly (at least 3 days per week) during the past 6 months. Characteristics of study participants are presented in **Table 1**. All names were amended and personal data disguised in order to maintain participants' anonymity. Participants were recruited to the quantitative study *via* social networks (Facebook, WhatsApp, etc.) and were included in the study if they served in a combat unit for at least 1 year (out of the three mandatory for men in Israel). Participants were excluded if they reported being prescribed medical marijuana during the past 6 months, due to the lack of validated measures assessing CUD in the medical context (17). Upon completion of the quantitative study, participants were asked if they were willing to participate in a face-to-face interview in case they qualify for the inclusion criteria of the qualitative phase, i.e., screening positive for a DSM-5 diagnosis of CUD.

Measures

Cannabis Use Disorder Identification Test Revised (CUDIT-R)

This instrument was used in the quantitative phase in order to screen for participants who qualified for a DSM-5 diagnosis of CUD, and were thus eligible for participation in the qualitative phase. The CUDIT-R is an eight-item self-report measure assessing problematic cannabis use during the past 6 months (e.g., "How often during the past 6 months did you need to use cannabis in the morning to get yourself going after a heavy session?"). Items were rated on a five-point Likert scale ranging between "0" (never) to "4." The sum score was automatically computed and a cut-off point of 6 was used to initially screen for a DSM-5 diagnosis of CUD (24). The CUDIT-R has previously shown good reliability ($\alpha = 0.914$ and $\alpha = 0.83$) in two separate samples (23, 24).

TABLE 1 | Personal characteristics of study participants ($N = 12$).

Name	Age[a]	Military service duration[a]	Military unit	Current status
David	22	3	Armored Corps	Musician
Jonathan	25	3	Infantry	Student in the social sciences
Guy	25	3	Infantry	Student in the social sciences
Tom	27	7	Special forces	Student in the social sciences
Eyal	25	3	Infantry	Teacher
Sharon	25	3	Combat intelligence	Engineering student
Avishai	27	3	Combat engineering	Student in the exact sciences
Alexander	26	3	Special Forces	Engineering student
Eilon	26	3	Armored Corps	Student in the human sciences
Michael	26	3	Infantry	Engineering student
Eden	31	8	Infantry	Student in engineering (MA level)
Noam	23	3	Armored Corps	Student in the social sciences

[a] *In years.*

Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 (AUDADIS-5)

A structured face-to-face diagnostic interview developed by the NIAAA and designed for lay interviewers. Among other issues, the AUDADIS-5 addresses DSM-5 substance use disorders. For the current study, the cannabis section of the AUDADIS-5 was used (25), which has previously shown good test-retest reliability for a past-year diagnosis of DSM-5 CUD (kappa $\geq$ 0.60) in a general population sample (26).

In-Depth Interviews

Interviews followed a timeline procedure (27), focusing on two timelines: (a) major positive and negative life events (b) trajectories of cannabis use, including initiation and cessation of cannabis use, increase/decrease in frequency of cannabis use and alleged onset of CUD (27). In order to allow participants to freely express their narratives, no topic list was used (28). However, interviewers emphasized three lifetime periods: (1) prior to military service, including early trauma, substance use during adolescence and expectancies toward military service (2) during military service, including training period and combat deployment, and (3) following release from duty, including adjustment to civilian life and major developmental stages during emerging adulthood.

Procedure and Analyses

Participants in the quantitative study, who qualified for a probable diagnosis of CUD (CUDIT-R $\geq$6) and who gave their consent for participation in the quantitative study, were approached *via* phone by one of the researchers or a research assistant. Time and place for the face-to-face interviews were set, and participants were requested to attend the interview while not under cannabis intoxication. Interviews were held primarily at the authors' offices, with duration ranging between 60 and 90 min. Prior to initiation of the interview, the AUDADIS-5 was administered in order to validate a probable diagnosis of DSM-5 CUD (i.e., meeting at least two CUD criteria). Two participants did not meet CUD diagnostic criteria according to the AUDADIS-5, and were therefore not included in the data analysis. Upon completion of the interview, participants were given 150 NIS (≒45 U.S Dollars).

All eligible interviews were audio recorded and transcribed while omitting personal details which could allow identification. Transcribed interviews were analyzed using the content analysis procedure (29), initially coding semantic segments and subsequently extracting a-priori and post-priori themes and meta-themes emerging from the interviews (22). In order to increase inter-rater reliability, initial coding was conducted by two independent raters (DF, MS) (30). Coding and theme extraction were conducted using the ATLAS.it software for qualitative data analysis. The study was approved by the Institutional Review Board (IRB) at Ariel University.

RESULTS

Data analysis has yielded the following themes, which will then be presented in detail below: (a) Traumatic events (b) Attitudes toward cannabis use (c) Combatant identity (d) The role of authority/father figures, and (e) Moral crisis (**Figure 1**). In line with our preliminary hypothesis, these themes followed a timeline, representing three major periods: prior to, during and following military service. **Table 2** describes frequency of the primary themes which emerged from the qualitative analysis. A meta-theme that has been identified is "from enchantment to disillusion." This meta-theme represents a narrative shift which is reflected in the extracted themes. This narrative shift represents a gradual psychological and behavioral transition from an "enchanted" stance, in which participants embraced and identified with values and norms associated with cannabis use, as well as personal and national military ethos. Eventually, participants' narratives reflected a sense of "disillusionment" from this identification, accompanied by an experience of mental and moral disenchantment.

Traumatic Events

A main, a-priori theme that emerged had to do with traumatic events and their effect on patterns of cannabis use. The majority of participants in our study were drafted into their service during Operation Protective Edge, which took place in Gaza strip in 2014, and was characterized by a relatively high number of IDF casualties. Its effects were repeatedly reflected in participants' narratives. For example, Tom recalled:

> *"Only a minute ago we hung out together, he was my friend… and then a moment later he's dead. And there was this guy who went to high school with me, and he's missing in action. And these three guys from my unit, great fellows, we used to spend a lot of time together, they're also killed. It's a deadly period, the worst that could possibly be, it's the first time that people I know go away and never return. It's a time when I understood that death is eternal."*

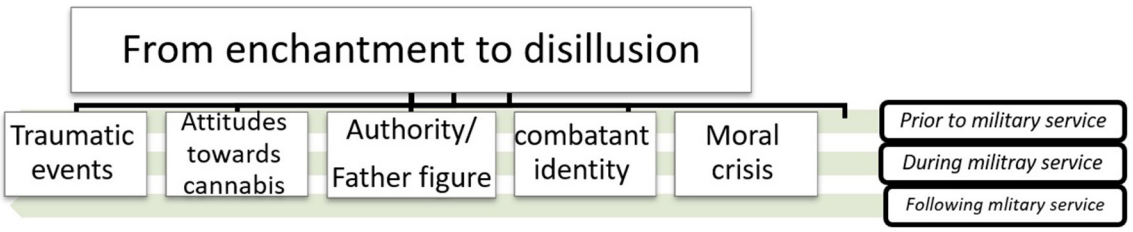

FIGURE 1 | Extracted themes and meta-theme.

TABLE 2 | Frequency of themes emerging from the qualitative analysis.

Theme		# Of participants who mentioned the theme
Traumatic events	During military service	6
	During operation protective edge	6
Cannabis: attitudes	Coping *via* cannabis use	10
	Ambivalent Stance	11
Authority	The role of the commander as a parental figure	4
	The role of the commander: disillusionment	10
Combat identity	High expectation toward military service	8
	Disappointment with military service	9
Moral crisis	Moral injury	5
	Sense of betrayal	11

Attitudes Toward Cannabis Use

All participants related to cannabis as a means for coping with life's adversities and traumatic events from their military service. The word "disconnection" repeatedly appeared when addressing the effects of cannabis use, echoing cannabis' role as a dissociative defense mechanism which allows participants to maintain such disconnection from traumatic memories and avoid mental pain.

> *"Cannabis makes me calm. I love this sort of disconnection. It allows me to sit down at the end of the day and say: 'I'm switched-off, I've forgotten everything that happened today.' If I don't smoke [cannabis] my thoughts run wild. When I smoke I just turn it off." (Jonathan)…"Why do I smoke? Because I want to take some time off from my life. To get away and lay down on a cloud of laughter, forget all my worries and hardships" (Sharon)*

Some of the participants specifically addressed cannabis use as a means for medicating trauma-related experiences. The most common was sleep disturbances, while others addressed the compensatory effect of cannabis:

> *"For a long time I could not sleep. It was hard for me and I tried all sorts of solutions. Cannabis made it better. It's not only more effective than other medications, but it also really works… I can finally sleep properly. For time to time there are tough nights, but it became a part of my life in a way that I don't think I'll ever want to quit" (Eyal)…"[Cannabis] allows me to cope with the losses I have suffered"* (David)…*"I told myself: I made it through this war [Operation Protective Edge], nothing happened to me. I didn't die, I'm not wounded, I deserve to do whatever I want"* (Guy)

As the interviews progressed, participants expressed an ambivalent stance toward cannabis. On the one hand, they addressed the regulatory function as a means for comprehending traumatic memories without being emotionally shaken. On the other hand, participants mentioned tolerance, psychological dependence and loss of control as common phenomena associated with cannabis use, and at times even fear of its negative long-term effects. Participants also mentioned that in some cases cannabis may increase their experience of negative emotions, such as anxiety, post-traumatic stress symptoms and anhedonia. In addition, a feeling that was portrayed is one of false wellness which emerges after prolonged cannabis use.

> *"I'm starting to feel bad about the weed. When you're weak you start to see its downsides. If we would have talked six months ago, I would say it's the best." (Michael)…"In a way I blame the cannabis. It gave me more anxiety, more worries, more demons, many things that I never had before. It brings me down a little. I know I blame it all on a plant, but I really think it has a big part in this"..."It makes you feel good in a false way, because at some point your body gets adjusted to the feeling. I feel I want to try and quit, I feel it turns my motivation down, the will, the passion. I don't like it when that happens. It turns my life off." (Avishai)*

Combatant Identity

Participants reflected on the high expectations that preceded their recruitment to combat units. Some emphasized the fulfillment of a national ethos, while for some becoming a combatant followed a family heritage and destination:

> *"At the beginning it was so exciting. My heritage. What my father kept talking about his entire life. His comrades and the strong bonds they have, this is something I wanted for myself." (Jonathan)…"Everyone would praise us, telling us how important we are to the country, telling us we're heroes, and all sorts of other clichés" (Sharon).*

However, the majority of participants experienced a deep sense of disappointment following their military service, accompanied

by feelings of distrust. Some participants talked about the discrepancy between their anticipation for an exciting and meaningful service, amplified by a national glorification of the Israeli combatant myth, and facing the monotonous, sometimes boring, military routine. Even while taking part in combat missions, a gap emerged between high expectations for flawless warfare and the disorganized, at times chaotic conduct of their combat unit:

> *"it gets tough when you realize you're not going to fight on a daily basis. I wanted to do more, but this routine of walking around doing nothing kind of brought me down" (Jonathan)… "So many mistakes have been made when it came to people's lives. I have a friend who died from a mortar bomb while sitting in a rally point. He only had two seconds to seek cover in some concrete cylinder that no one can really squeeze himself into. This just isn't right" (Eyal).*

Role of Authority/Father Figures

It appears as though a part of the anticipation toward military combat service had to do with the image of command. Several participants related to the commander as a parental figure whose responsibility over his subordinates was absolute. Notably, this followed participants' personal biography, as some grew up with a dominant father figure, while others reported being deprived of a close relationship with a father figure:

> *"He's [the commander] in charge of 20 soldiers. It's a matter of life and death, so he has to be their father. He's in charge of everything and if he's dysfunctional, he has to have a good reason for that" (Tom)... "I wanted to be posted exactly where my father was, go to the same places as he did, as a paratrooper" (Jonathan).*

These expectations toward their commander were often faced with a disillusioning reality in which commanders failed to be flawless, and at times were perceived as unfair, irresponsible and ego-driven:

> *"There are several troop leaders who have lost their humanity and trampled me along the way. Let's just say that during Operation Protective Edge, the most negative psychological experiences I had are related to the way I was treated by commanders, not to what I have seen in action"(Guy)… "The commander yelled 'casualties!', so being a paramedic I took my stretcher and ran like crazy to see who's injured. I was certain there's someone dying out there, but it turned out to be a drill, a way to see how we respond. What a cruel trick to pull" (David).*

Moral Crisis

During the interviews, participants often recalled morally injurious events from their military service. These events seem to create a prolonged tormenting conflict between participants' internalized moral values and the immoral deeds they were bound to perform as soldiers. In some cases, immoral conduct emerged from the paradoxical nature of the battlefield, while in other cases participants were ordered to perform immoral acts. At times, moral injury has occurred while in action, and in some cases it emerged later on after their release from duty. For many of the participants, these "faulty events" remain an unsettled business, accompanied with shame and guilt, which still echo in their daily life, self-perception and their desire to self-medicate:

> *"I felt like I lost my identity while on duty. I used to look at myself in mirrors of the houses we seized in Gaza, and I got sick of seeing my face camouflaged, hearing little girls cry. I was like a mission contractor during these years, and it left its mark, I've lost my innocence back there" (Tom)… "90% of the time using such brutality was uncalled for. Punching someone just to keep him silent. For six months I would go out at night, see some farmer and chase him down with two assault dogs, only because he was allegedly filming and spying on us. But I don't believe it. This is what they [commanders] would tell me to do and I had to do it, but it felt faulty to me most of the time" (Avishai)… "*

DISCUSSION

In this study we explored narratives of Israeli veterans who were recently released from military duty and are currently qualified for a diagnosis of CUD. Major themes that emerged were related to trauma and moral crisis associated primarily with military-related events, as well as an ambivalent stance toward cannabis use, combatant identity and authority/father figures. A meta-theme that has emerged, encompassing these themes, is participants' gradual transition from enchantment to disillusion, resulting in a current cannabis-related pathology accompanied by an ambivalent representation of their military service.

In our study, trauma has emerged as a primary theme, and one that is highly concurrent with cannabis use. Previous findings have indicated that post-traumatic stress response and PTSD are very common among combat veterans and are highly comorbid with cannabis use and CUD (12). High comorbidity is also present within the general population, with epidemiological findings associating childhood adverse events and PTSD incidence with higher odds for CUD onset (5). A key motivation for cannabis use presented by participants in our study was regulating or coping with negative emotions associated with traumatic events and moral injury. This is in line with numerous reports indicating that relief from negative emotional experience is a primary motivation for cannabis use (31–33). The short-term effects of cannabis use often include psycho-physical stress reduction and reinforcing psychoactive effects which allow for a shift in attention away from the aversive emotional state (34). Therefore, it is understood why ex-combatants, often haunted by their traumatic past and conflicted present, may wish for the temporary comfort in cannabis use.

Despite its beneficial short-term effects on negative emotions, coping-oriented motives for cannabis use may in fact be harmful in the long-run. For example, coping motives for cannabis use have been associated with an increased risk for CUD onset (35, 36). It is often suggested that individuals may turn to substance use in order to compensate for their impaired or

insufficient innate self-regulatory mechanism (33), eventually developing pathological patterns of substance use. While reward-driven motivation has been historically associated with the neuro-etiology of substance use disorders, it is now accepted that negative emotional states play a key role in the transition from substance use to SUD (37). By triggering negative rather than positive reinforcement, negative emotions may trigger compulsive or chronic use of substances, including cannabis (38–40). Thus, it may well be that veterans who cope with traumatic events and moral injury "self-medicate" their distress by using cannabis (41), are eventually inclined to develop CUD due to chronic dysregulation in reward and regulatory functions (42, 43).

In addition to the risk of developing CUD, participants emphasized the paradoxical nature of cannabis use in medicating post-traumatic stress symptoms. Despite accumulating evidence of the beneficial effect of cannabis use on sleep disturbances associated with PTSD (16, 44), cannabis use appears to be ineffective in long-term reduction of the majority of PTSD symptoms (45). Among heavy users, cannabis use may even be associated with a poorer PTSD outcome, namely increase in intrusive symptoms severity (46). While being generally ineffective in treating PTSD symptoms severity, veterans who use cannabis may be exposed to additional long-term adverse effects, such as panic attacks, psychotic episodes, cognitive deficit, etc. (12, 47).

Additional themes that emerged had to do with participants' disillusionment from a personal and national ethos related to the military, as well as a moral crisis associated with combat-related events. Several authors have emphasized the role of a sense of betrayal in the formation of moral injury among combatants and ex-combatants. In these cases, a deep sense of distrust may develop toward commanders and/or leaders, who are perceived as betraying 'what is right' in high stakes situations (14). A sense of betrayal is thought to increase vulnerability to post-traumatic stress symptoms, and at times provoke anger, hostility and aggression (14, 15). In some cases, betrayal may lead to shame, guilt and forms of self-destructive behaviors, including suicidality and frequent substance use (13, 48).

From a psychodynamic perspective, trauma may emerge from significant others' failure to provide a psychologically adequate environment for the development of a coherent and cohesive sense of self-esteem (49). Substance use is often conceptualized as an effort to medicate for an unstable or deprived sense of self-esteem (50). Therefore, it may well be that the transition reported by participants in their self-perception, from "heroes" to "mission contractors," as well as their perception of authority figures, shifting from "parents" to "inhumane," may result in an existential crisis which is compensated by excessive cannabis use (51, 52).

This study has several limitations that should be considered. First, the qualitative nature of the study doesn't allow for exploring statistical and causal association between variables, as well as for the generalization of the findings beyond the study participants (53). Second, being a qualitative study, the present investigation is influenced substantially by the subjective experience of participants, investigators and their interaction (54). Third, the relatively small sample may have halted the emergence of additional themes related to cannabis use and its psycho-social correlates. In addition, the lack of a control group, comprised of age-and-gender matched non-cannabis users or non-combat veterans who use cannabis, undermines the specificity of our findings. Fourth, this investigation focused on newly released, exclusively male combatants of Jewish ethnicity. Therefore, findings could not be generalized to older combat veterans, as well as non-Jewish veterans (Christian, Bedouin, Druze, etc.) and female veterans. The latter constitute ∼2% of current combatants in the IDF and a growing proportion in the U.S. military. Female combatants' unique combat-related experiences are drawing increased scientific attention (55, 56) and should be subject to future exploration in the context of cannabis use and CUD.

Despite these limitations, the increase in the global prevalence of cannabis use and CUD, both within the general population and among veterans, as well as the emerging changes in cannabis' legal status, call for integrative research into the psychosocial predictors of CUD. Further exploration of veterans' narratives regarding cannabis use and CUD is needed in order to trace the etiology of CUD within this population. Themes that emerged from our study can be used for further quantitative investigation of underlying risk factors for CUD. The role of personal and national disillusionment, moral injury and the role of authority in predicting CUD among combat veterans should be explored in future large-scale longitudinal studies, thus allowing for better prevention, assessment, and treatment for those who develop pathological patterns of cannabis use.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Dr. Ephraim Grossman, Department of Education, Ariel University, Ariel, Israel. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MS and DF: acquisition of data, analysis and interpretation of data, drafting the article, and final approval of the version to be submitted. SS-G: conception and design, analysis and interpretation of data, revising the manuscript critically for important intellectual content, and final approval of the version to be submitted. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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Precision Mental Health Care for Cannabis Use Disorder: Utility of a bioSocial Cognitive Theory to Inform Treatment

Matthew J. Gullo[1,2*], *Zoë E. Papinczak*[1,2,3], *Gerald F. X. Feeney*[1,2], *Ross McD. Young*[1,2,4] *and Jason P. Connor*[1,2,5]

[1] National Centre for Youth Substance Use Research, The University of Queensland, Brisbane, QLD, Australia, [2] Alcohol and Drug Assessment Unit, Princess Alexandra Hospital, Brisbane, QLD, Australia, [3] School of Psychology, The University of Queensland, Brisbane, QLD, Australia, [4] Jamieson Trauma Institute, Metro North Health, Herston, QLD, Australia, [5] Discipline of Psychiatry, Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia

Globally, cannabis is the most frequently used controlled substance after alcohol and tobacco. Rates of cannabis use are steadily increasing in many countries and there is emerging evidence that there is likely to be greater risk due to increased concentrations of delta-9-tetrahydrocannabinol (THC). Cannabis use and Cannabis Use Disorder (CUD) has been linked to a wide range of adverse health outcomes. Several biological, psychological, and social risk factors are potential targets for effective evidence-based treatments for CUD. There are no effective medications for CUD and psychological interventions are the main form of treatment. Psychological treatments based on Social Cognitive Theory (SCT) emphasize the importance of targeting 2 keys psychological mechanisms: drug outcome expectancies and low drug refusal self-efficacy. This mini-review summarizes the evidence on the role of these mechanisms in the initiation, maintenance, and cessation of cannabis use. It also reviews recent evidence showing how these psychological mechanisms are affected by social and biologically-based risk factors. A new *bioSocial Cognitive Theory (bSCT)* is outlined that integrates these findings and implications for psychological cannabis interventions are discussed. Preliminary evidence supports the application of bSCT to improve intervention outcomes through better targeted treatment.

Keywords: reward, impulsivity, expectancies, self-efficacy, cannabis, social cognition, *bioSocial Cognitive Theory*, precision medicine

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***Correspondence:**
Matthew J. Gullo
m.gullo@uq.edu.au

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INTRODUCTION

Cannabis is the most widely used illicit drug worldwide and more jurisdictions are decriminalizing or legalizing use (1, 2). In 2018, it was estimated that 3.9% of the global adult population reported past-year cannabis use [∼192 million people (3)]. North America (12.4%), West and Central Africa (12.4%), and Oceania (10.3%) are among the highest cannabis-using regions in the world, with rates of use increasing in many nations (3). Cannabis may be more harmful now than it has ever been, due to increased *delta-9-tetrahydrocannabinol* (THC) content—the key psychoactive ingredient (3–5). Higher THC potency cannabis is associated with an increased incidence of adverse side effects (6, 7).

The most severe and likely adverse side effect of cannabis use is developing a Cannabis Use Disorder [CUD; (8)]. Of those who have ever tried cannabis, 1 in 10 will develop moderate-severe CUD, formerly labeled *cannabis dependence* in the DSM-IV (9, 10). This risk increases to 1 in 6 if use commenced during adolescence (11). Daily users hold the greatest risk with ∼1 in 2 developing moderate-severe CUD (12). Moderate-severe CUD impacts several areas of functioning with those affected more likely to experience comorbid psychiatric problems, relationship and financial difficulties, insomnia, withdrawal symptoms, reduced energy, low self-esteem and self-confidence, and reduced productivity (13–15). There are no effective medications for CUD and psychological interventions are the main form of treatment (2, 16).

The effectiveness of *cognitive-behavior therapy* (CBT), *motivational enhancement therapy* and *contingency management* as treatment for CUD is well-established [e.g., (16–18)]. CBT for substance use disorder and, to a lesser extent, motivational enhancement therapy with its focus on self-efficacy, are based on Social Cognitive Theory (SCT) (19). Social Cognitive Theory (SCT) conceptualizes cannabis use as a learned behavior that is believed to serve some adaptive and coping functions (e.g., stress reduction, social facilitation). CBT targets the (perceived) functional role that cannabis use plays in a patient's life and seeks to alter the cognitive and behavioral mechanisms precipitating use (20, 21). Patients are taught skills to aid cannabis reduction/cessation and maintain this change. This could involve, for example, teaching patients to identify situations likely to trigger motivation to cannabis use and how to avoid them, or how to address the thoughts and emotions underlying the motivation to use (22, 23). Other components of CBT include building drug refusal skills and problem-solving skills, and making healthy lifestyle modifications (24). The main goals of CBT are to increase patient self-efficacy to resist cannabis use and expand their repertoire of coping skills (21). While effective, CBT and other evidence-based treatments produce modest long-term outcomes in moderate-severe CUD (25–27), less than one third of those with CUD seek treatment and, among those, almost half prematurely discontinue treatment (26, 28–31). Further refinement of effective treatments like CBT could lead to improved patient retention and outcomes. The aim of this mini-review is to summarize the evidence on key psychological mechanisms in CUD and how they are affected by social and biologically-based risk factors. A theoretical review was conducted on published studies of Social Cognitive Theory and cannabis use, encompassing related relevant literature on other drug expectancies, self-efficacy, and temperament/personality. There were no a priori restrictions on the type of published studies included. In integrating these findings, a new *bioSocial Cognitive Theory (bSCT)* is reviewed that could facilitate a more precise application of evidence-based treatments like CBT.

SOCIAL COGNITIVE THEORY

In its application to substance use, SCT predicts that the likelihood of using substances is the result of an individual's drug outcome expectancies and refusal self-efficacy beliefs (32–34). These beliefs can develop through vicarious conditioning (observing others), even before substance use is initiated (19). Individuals who have never used cannabis already hold beliefs about the expected positive and negative outcomes of use, which are called cannabis outcome expectancies, and these beliefs predict future use (35–37).

Cannabis Outcome Expectancies

Cannabis outcome expectancies are beliefs that an individual holds regarding the expected consequences of engaging in cannabis use, which may be positive or negative (19, 37). Positive cannabis expectancies play an influential role in motivating substance use, whilst negative expectancies generally serve to inhibit use (35, 37–40). Their effect on cannabis use behavior may not be equal. Some studies have found negative cannabis expectancies are no longer associated with consumption when controlling for the effects of positive expectancies (37, 39, 41). Negative expectancies are also a stronger correlate of cannabis-related problems in clinical samples. Therefore, high negative expectancies may be more the result of problematic cannabis use rather than low negative expectancies being an initial cause (37, 41–43).

Expectancies affect motivation to attempt, and ability to succeed in, cannabis cessation. Positive cannabis expectancies are associated with less positive *cessation* expectancies (i.e., beliefs that quitting cannabis will result in positive outcomes), while negative expectancies are associated with more positive cessation expectancies and perceived benefit of reducing use (44, 45). Boden et al. (39) found baseline positive cannabis expectancies predicted greater odds of lapse/relapse during a self-initiated cessation attempt in military veterans with CUD. Negative expectancies predicted lower odds of lapse/relapse. In moderate-severe CUD outpatients, Gullo et al. (46) found that higher levels of negative expectancies predicted greater likelihood of abstinence and fewer days of use over 6 weeks of CBT. While positive expectancies did not directly influence cannabis use, their effect was fully mediated by a negative association with cannabis refusal self-efficacy. That is, positive expectancies may increase relapse risk by undermining confidence in the ability to resist cannabis in cued situations.

Cannabis Refusal Self-Efficacy

Cannabis refusal self-efficacy is the confidence that an individual has in their ability to resist or refuse using cannabis in cued situations (47). Generally speaking, the strength of self-efficacy beliefs determine whether a person will attempt to cope with a difficult situation and how much effort is exerted (19, 48). Cannabis refusal self-efficacy plays an important protective role at several stages of cannabis use. For instance, high levels of cannabis refusal self-efficacy are associated with non-use in adolescents (49–51). Among frequent cannabis users, high levels of refusal self-efficacy are associated with fewer cannabis-related problems, less severe dependence and fewer days of use (41, 42, 47, 52).

Cannabis refusal self-efficacy may play a role in motivating behavior change among heavy cannabis users. One study found that cannabis refusal self-efficacy was associated with greater

readiness to change, and predicted initiation of behavior change among men with cannabis dependence (53). Another study revealed that in female users who had previously tried to quit cannabis, refusal self-efficacy was associated with greater motivation to try again (54). These findings are consistent with Bandura's (19, 48) conceptualization of self-efficacy whereby individuals are more likely to engage in behaviors in which they are confident that they can enact successfully.

Cannabis refusal self-efficacy is consistently associated with better treatment response. Pre-treatment levels of cannabis refusal self-efficacy are associated with greater odds of abstinence during CUD treatment (46, 53) and predict less cannabis use and fewer cannabis-related problems for up to 6 months post-treatment (55). Post-treatment levels of cannabis refusal self-efficacy have an even stronger positive effect, predicting less cannabis consumption at 3, 6, and 12-months post-treatment (56–58). Low self-efficacy in response to negative emotion may be particularly salient (46).

Cannabis refusal self-efficacy may also be an important mechanism of change in treatments for CUD. Several studies have demonstrated that changes in cannabis refusal self-efficacy that occur during treatment are the strongest predictor of long-term abstinence—up to 14 months (25, 56–58). Regardless of specific treatment received, individuals who report the greatest improvements in cannabis refusal self-efficacy in treatment experience the most successful outcomes (33, 58, 59). These results indicate that increased cannabis refusal self-efficacy is a mechanism of change in psychological treatments for CUD.

One study has examined the means through which cannabis refusal self-efficacy may translate into improved treatment outcomes. Litt and Kadden (58) combined data from 3 cannabis treatment trials ($N = 901$) and found that the effects of refusal self-efficacy on cannabis use and cannabis-related problems were partially mediated by increased use of coping skills and by reductions in emotional distress. These findings support Bandura's (19, 48) hypothesis that self-efficacy determines whether a person will attempt to cope with a difficult situation and how much effort is exerted. However, the indirect/mediated effects reported by Litt and Kadden were small and the larger direct effects of self-efficacy remained unexplained. Further research is needed to obtain a better understanding of precisely how increased self-efficacy leads to better treatment outcomes.

Consistent with Bandura's (19, 48) contention that self-efficacy is the final pathway that influences human behavior, cannabis refusal self-efficacy has been found to mediate the effects of other psychological risk factors on cannabis use and related problems: cannabis outcome expectancies, cannabis coping motives and descriptive peer norms (41, 46, 52, 60). Despite the importance of cannabis expectancies and refusal self-efficacy, there is a paucity of research examining these constructs together. This is also true of the wider substance use literature. Theoretically, outcome expectancies should affect refusal self-efficacy in the development of CUD (33). For example, an individual expecting greater reinforcement from cannabis (high positive expectancies) is more likely to believe it to be harder to resist in cued situations (low refusal self-efficacy). The impact of cannabis expectancies on consumption is likely to be mediated in large part by self-efficacy, and this has been demonstrated empirically (41, 46).

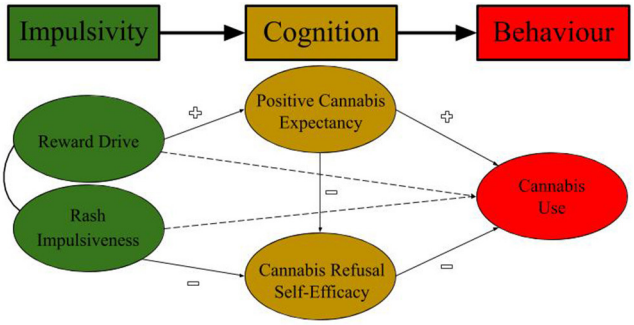

FIGURE 1 | bioSocial Cognitive Theory (bSCT) of Cannabis Use.

In summary, SCT provides a valuable framework to conceptualize CUD and already informs evidence-based treatments. Empirical studies of SCT applied to cannabis use show that the aggregate positive outcomes an individual expects from cannabis, the more likely they are to engage in problematic use. Conversely, the stronger the negative outcomes expected and the more confident that an individual is in their ability to resist using cannabis, the more likely they are to abstain. Positive cannabis expectancies may have a stronger impact on behavior than negative expectancies. However, the important role of refusal self-efficacy as a mediator of expectancy effects complicates simple interpretations, and there is a need for more integrative research to advance the field. Increasing self-efficacy is a primary goal of existing evidence-based treatments. A better understanding of the factors that strengthen refusal self-efficacy could serve to improve upon them.

bioSOCIAL COGNITIVE THEORY OF TEMPERAMENT, OUTCOME EXPECTANCIES, AND REFUSAL SELF-EFFICACY

Individual differences exist in the strength of one's drug outcome expectancy and refusal self-efficacy beliefs. According to Bandura's (19, 48) notion of triadic reciprocal causation, these beliefs are influenced by, and in turn influence, one's *behavior*, their *environment* and *personal factors* within the individual. Gullo et al. (61) proposed that, when applied to substance use, biologically-based personality traits, specifically reward sensitivity/drive and rash impulsiveness, should act as important personal factors affecting social cognition and behavior (61). These traits are robust predictors of cannabis use (62, 63) and studies have found selective associations between reward drive and positive cannabis expectancies on the 1 hand, and rash impulsiveness and cannabis refusal self-efficacy on the other (51, 64). This *bio*Social Cognitive Theory (bSCT) of temperamental risk factors, outcome expectancies, and drug refusal self-efficacy is depicted in **Figure 1**.

Reward drive reflects individual differences in one's sensitivity to reward stimuli and subsequent motivation to approach and obtain them, including substances (65–67). Individual differences in reward drive are biologically-based, reflecting variation in mesolimbic dopamine system functioning (68–70). Higher reward drive predicts greater reactivity to substance-related cues and unconditioned responses to their ingestion (71–75). As a result, individuals high in reward drive are more likely to attend to, encode, and recall reinforcement from cannabis use, creating stronger positive outcome expectancies. Studies of young adults and cannabis users referred to treatment have indeed observed a selective association between individual differences in reward drive and positive cannabis expectancies (51, 64). In moderate-severe CUD, positive expectancies are related to poorer treatment response because of their association with lower refusal self-efficacy (46).

Rash impulsiveness reflects individual differences in the capacity to inhibit/modify prepotent approach behavior in light of potential negative consequences (65, 67). Individual differences in rash impulsiveness are biologically-based, reflecting variation in the functioning of the orbitofrontal and anterior cingulate cortices (70, 76–78). Higher rash impulsiveness is associated with poorer reversal learning (79, 80), inhibitory control deficits in substance-dependent individuals (81), and mediates behavioral disinhibition associated with a family history of alcohol use disorder (82, 83). Individuals high in rash impulsiveness are typically aware of their difficulties with inhibitory control, which increases the likelihood of developing a generalized lower self-efficacy for situations requiring reward refusal, including substances (80). This lowered self-efficacy, in turn, increases the likelihood of cannabis use, further exacerbating risk (48). Studies of young adults and cannabis users referred to treatment have indeed observed a selective association between individual differences in rash impulsiveness and lower refusal self-efficacy (51, 64). In moderate-severe CUD, lower cannabis refusal self-efficacy predicts poorer response to treatment (46, 58).

DISCUSSION

Toward Precision Mental Health Care for Cannabis Use Disorder

The etiology of CUD is complex and several risk factors have been identified. bioSocial Cognitive Theory (bSCT) synthesizes some of the key risk factors in a way that may help practitioners better understand their combined and interacting effects, including how they manifest in the patient in front of them. This understanding is essential to optimizing treatment (i.e., precision mental health care (84, 85)]. In this mini-review, our focus started in the clinic with an established treatment (CBT) and its proposed mechanism of action (social cognition). We then broadened this focus to incorporate biologically-based factors theorized to directly affect these modifiable mechanisms (impulsivity traits). In outlining the interactions between these biological and cognitive factors, and their effect on behavior, bSCT can reveal individualized targets for CUD treatment.

bioSocial Cognitive Theory (bSCT) proposes modifiable pathways of risk that may be altered directly or indirectly during CUD treatment for different patients. For example, while it is known that increasing refusal self-efficacy is important, the most effective means of doing so will vary between patients (33, 58, 86). Directly increasing it with refusal skills training will work for patients who need to learn skills in how to assertively say "no" when offered or pressured to use cannabis (87, 88). But, according to bSCT, it is less likely to be effective in isolation for those high in rash impulsiveness and holding strong positive expectancies (51, 64). Such patients would be likely to face more significant challenges saying "no" in the first place, because of the greater salience of expected short-term reinforcement (e.g., intoxication) and lesser salience of future negative consequences (e.g., negative urine drug test result at work). For these patients, cognitive restructuring to reduce positive expectancies and strategies to increase reflection and problem-solving would be indicated, according to bSCT. An assessment of patient bSCT factors could reveal high-value therapeutic targets, facilitating tailored treatment.

As a proof-of-concept for bSCT's utility in precision mental health care, Papinczak et al. (89) drew on bSCT to develop a theoretically-driven instant assessment and feedback system (iAx) for CUD. iAx electronically administers and instantly scores validated, standardized assessments and synthesizes this information through the theoretical lens of bSCT. Compared to treatment-as-usual, which administered the same assessments, iAx-enhanced brief intervention led to significantly greater motivation to reduce cannabis use in 87 non-treatment seeking users referred for assessment. Papinczak et al. proposed that iAx may have improved practitioners' formulation of the case, increasing treatment precision. Amidst a sea of assessment results, iAx may have provided a clearer focus on the modifiable factors likely to maximize outcomes for that patient. A CUD and alcohol use disorder version of iAx is now freely available at gullo.com.au/iaxsite.

This mini-review summarizes evidence on the application of bioSocial Cognitive Theory (bSCT) to cannabis use disorder (CUD). Findings are encouraging and consistent with those previously reported in alcohol use disorder (61, 90–92). Further examination of temporal dynamics and reciprocal causation would strengthen clinical application, as there is some evidence of differences in bSCT pathway strength across the continuum of addiction (51, 64). The role of craving is also yet to be explicitly outlined, despite its importance to CUD. Recent developments in cognitive theories of craving and its measurement will facilitate integration (93, 94). There is also scope for inclusion of more fundamental biological factors, such as genetics, building on earlier work in SCT (95, 96), identification of genetic associations with impulsivity and psychiatric comorbidity (97, 98), and incorporating recent methodological advances [e.g., polygenic risk scores (99)]. However, the utility of bSCT in its current form is clear. It provides a coherent theoretical framework for integrating SCT and impulsivity theories of addiction, pointing toward new avenues for targeted treatment. bSCT constructs are predictive of CUD risk, motivation to seek treatment, and response to treatment. Preliminary evidence shows that simply

presenting clinical assessment data through the lens of bSCT enhances delivery of brief intervention. These are valuable initial steps toward developing greater precision in the treatment of CUD.

AUTHOR CONTRIBUTIONS

MG and ZP created the outline of the review and wrote the first draft. ZP conducted the literature review. All authors contributed to subsequent revisions and approved the final manuscript.

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The Effects of Cannabis Use Frequency and Episodic Specificity Training on the Recall of Specific and Rewarding Events

*Michael J. Sofis, Shea M. Lemley and Alan J. Budney**

Center for Technology and Behavioral Health, Geisel School of Medicine, Dartmouth College, Lebanon, NH, United States

Background: Growing evidence implicates subjective episodic memory, the retrieval of detailed, integrated, and personally relevant past events, as a marker of cognitive vulnerability in mental disorders. Frequent and problematic cannabis use is associated with deficits in objective episodic memory (verbal memory), but the relationship between subjective episodic memory deficits and frequency of cannabis use is unknown. Further, whether a brief intervention designed to enhance the specificity of event retrieval, such as the Episodic Specificity Induction (ESI), might effectively target such deficits among regular cannabis users is unexamined. This study was designed to examine subjective episodic memory as a potential marker of cognitive vulnerability among frequent cannabis users.

Methods: Active cannabis users (n = 133) recruited from Amazon Mechanical Turk or Qualtrics Panels were randomized to receive an ESI-control or ESI session and were separated into those who used cannabis 1–25 days in the past month (low to moderate frequency group) and those who used 26–30 days (high frequency group), which facilitated a low to moderate use/ESI-control group (n = 78), low to moderate use/ESI group (n =15), high-use/ESI-control group (n = 20), and high-use/ESI group (n = 20). Following the ESI or ESI-control intervention, participants selected four, positive events from the prior day, described the who, what, and where of the events, and rated how specific (vividness) and rewarding (enjoyable, importance, and exciting) each event was on a 0–100 scale. Four two-way ANCOVAs (demographics and problematic cannabis use covariates) were performed to examine the effects of frequency of cannabis use group and ESI group on the specificity and reward ratings.

Results: Lower vividness and excitement ratings were reported for those with high relative to low to moderate cannabis use frequency patterns ($p < 0.05$). Those who received ESI reported greater vividness, excitement, and importance ratings than the ESI-control group ($p < 0.01$). No significant interactions between frequency and ESI were found.

Conclusion: Findings from the current exploratory study provide initial evidence suggesting that more frequent cannabis use may be associated with the retrieval of less

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Eva Hoch,
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Sara Liane Kroll,
Linköping University, Sweden

****Correspondence:***
Alan J. Budney
alan.budney@dartmouth.edu

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specific and rewarding events relative to less frequent users. Further, ESI may improve such deficits. Future studies that recruit larger and more clinically serious samples of cannabis users appear warranted.

Keywords: cannabis (marijuana), episodic memory (EM), episodic specificity induction, reward, cannabis use disorder

INTRODUCTION

Episodic memory, defined as the capacity to retrieve details of personal past events (1), is often sub-categorized as either a form of verbal memory (e.g., accurately recalling when you last spoke to a friend; objective episodic memory); or as the retrieval of detailed, integrated, and personally relevant past events [e.g., recalling the sensory, affective, and contextual details of when you last spoke to a friend; subjective episodic memory; (2)]. Deficits in subjective episodic memory are associated with a tendency to overlook specific contextual details in favor of overgeneralizing experiences into a single theme or central meaning (3). This failure to retrieve detailed characteristics of past events may inhibit the ability to vividly re-experience positive past events, simulate positive future events, and is associated with more frequent rumination, avoidance behaviors, and cognitive biases (4–6). Such deficits have been shown to predict the trajectory and the response to treatment in those with Major Depressive Disorder, Post-Traumatic Stress Disorder, and Schizophrenia (7–9). Moreover, interventions that prompt the practice of recalling detailed past events have been shown to improve the specificity of event retrieval and may mediate the effects of specificity training on reductions in depression symptoms (6). These findings suggest that specificity of event retrieval may function as a marker of cognitive vulnerability for mental disorders and that interventions which effectively target this construct may help improve treatment for clinical disorders associated with episodic memory deficits.

Frequent cannabis use and Cannabis Use Disorder (CUD) have been associated with risk for developing moderate to large deficits in objective episodic memory (10, 11). Laboratory studies have demonstrated a dose-dependent relationship between acute cannabis administration and performance on objective episodic memory tasks, and longitudinal studies have shown that within-person increases in frequency or severity of cannabis use problems correspond with greater decrements in objective episodic memory (11–14). Few, if any studies, however, have explored the relationship between subjective measures of episodic memory and cannabis use. It may be important to address such a gap in the literature because deficits in the ability to retrieve salient past events among those who use cannabis frequently corresponds with problems evaluating past events as rewarding. Further, less specific and rewarding retrieval of past events relates to greater devaluation of future rewards, known as delay discounting (DD), which is a risk factor associated with more frequent and problematic cannabis use and which has been shown to predict treatment outcomes for CUD (15–17). Reduced specificity when recalling past events also negatively impacts the ability to simulate detailed and rewarding future events (18), which may contribute to deficits in problem-solving and planning commonly observed in those who engage in frequent or problematic cannabis use. However, there is a need to test whether frequent cannabis use is associated with deficits in subjective episodic memory. Moreover, to better understand whether subjective episodic memory deficits may function as a treatment target for interventions that seek to reduce cannabis use, there is a need to examine whether subjective episodic memory can be enhanced in those who regularly use cannabis.

Episodic Specificity Induction (ESI) is a brief intervention that has been effectively used to enhance the specificity of event retrieval (1, 19). Episodic Specificity Induction prompts recollection of episodic details derived from a brief video through guided questions that increase the specificity of mentally constructed events (19). Episodic Specificity Induction has been shown to enhance the amount of detail individuals can recall from past events, which in turn may contribute to increases in positive affect and decreases in negative affect in healthy individuals (20). Episodic Specificity Induction has also shown to increase the number of alternative future events constructed during a simulation task (21). To date, no studies have explored how ESI affects subjective episodic memory in those who regularly use cannabis.

To test whether more frequent cannabis use is associated with deficits in subjective episodic memory, we compared event retrieval responses (i.e., reward and specificity ratings) between those with low to moderate relative to high frequency cannabis use patterns following an ESI intervention or an ESI control condition. We hypothesized that (1) those who used cannabis more frequently would retrieve less specific and rewarding events relative to those with less frequent use, and (2) that ESI would enhance specificity and reward ratings relative to ESI control. Lastly, we examined whether there was a significant interaction between ESI condition and frequency of use groups (low to moderate vs. high) such that ESI would enhance subjective episodic memory measures to a greater extent in high frequency relative to low to moderate frequency cannabis users. If observed, this would provide support that ESI may be a particularly helpful intervention for targeting subjective episodic memory deficits in among more frequent cannabis users. The goal of this study was to provide an initial validation for the role of subjective episodic memory as a potential treatment target for novel interventions designed to reduce cannabis use.

METHODS

Procedures

The Institutional Review Board from Dartmouth College approved all procedures. All study sessions were administered

remotely using Qualtrics survey software and participants were recruited using the crowdsourcing platform Amazon Mechanical Turk (mTurk) or Qualtrics Panel participants. All data described in the current study were derived from a single intervention session conducted in one of two studies.

Participants ($n = 133$) completed an ESI-control (*ESI-c)* session ($n = 98$; Study 1) or an *ESI* session ($n = 35$; Study 2). All intervention components that were administered across both studies were the same. mTurk participants who completed either study earned up to $7.50. Qualtrics Research Panel participants were compensated via standard procedures for the panels (exact amount varied and was unknown to us), however, Qualtrics representatives indicated that the compensation was similar in magnitude to that of our mTurk participants.

Participants

Participants were recruited from Amazon Mechanical Turk (mTurk), an online crowdsourcing marketplace, in Study 1, and from both mTurk and Qualtrics Research Panels in Study 2. To be eligible for mTurk recruitment, workers participants had to have a 95% or higher approval rating on all previously submitted mTurk HITs and to have completed at least 100 Human Intelligence Tasks (HITs). Inclusion criteria for both sources included: reside in the U.S, age 18 or older, used cannabis in the last month (Study 1) or at least 10 days in the past month (Study 2), and used cannabis at least 100 lifetime days. To be inclusive of older cannabis users who increasingly use cannabis, participants older than 65 were included in the study to facilitate recruitment of a larger sample size. However, given previous evidence of age-specific differences in episodic memory (1), we controlled for age in the primary models conducted for this study. Within each of the two studies, participants were excluded if they missed two or more of three total attention checks or showed inconsistent responding.

Episodic Specificity Induction

Episodic Specificity Induction prompted recollection of episodic details through open-ended text responses related to the who (e.g., "Who was in the video?" "What were they wearing?"), what (e.g., "What was the video about?"), and when ("In what order did the events of the video occur?") of the video (1, 22). The ESI involves watching a 2-min video of a woman giving a tour of her tiny house, and participants could not move to the next step in the training until the entire 2-min had elapsed (22). Participants then type answers to each of seven questions about episodic details from the tiny house video (e.g., "What did the people in the video look like?," "What happened in the video, in order?").

Episodic Specificity Induction-Control

Those in the ESI-c component watched the same tiny house tour video as those in the ESI condition. Unlike the ESI condition, those in the ESI-c condition answered seven questions designed to prompt semantic (external) details related to the video to control for the attention of participants and so that only the type of retrieval (episodic vs. semantic) was manipulated (e.g., "What did you think about the setting of the video?," "How do you think it [the video] was made?").

TABLE 1 | Demographic and participant characteristics.

Demographic variables	*Overall*	*ESI-c (n = 98)*	*ESI (n = 35)*	*p*
Age *(M, SD)*	36.4 (11)	34.4 (1.1)	42.7 (2.3)	<0.01[a]
Gender *(n, %)*				
Female	127 (48%)	48 (49)	21 (60)	0.30
Level of education *(n, %)*				
College degree	135 (52)	52 (53)	14 (40)	0.33
Employment (*n*, %)				
Full-time		71 (72)	18 (51)	<0.01[a]
Cannabis use variables				
CUD *(n, %)*	140 (54)	56 (57)	18 (51)	0.68
Readiness to change *(M, SD)*	2.3 (2.5)	2.1 (2.5)	2.5 (1.7)	0.57
Days of use *(Mdn)*	10–19	6–9	26–29	<0.01[a]

"Mdn" represents the exact median, "M" represents the mean, and "SD" represents the standard deviation. "CUD" indicates the proportion of participants who meet the cutoff score for screening positive for Cannabis Use Disorder (CUD) using the Cannabis Use Disorder Identification Test Short-Form (CUDIT-SF). "Readiness to Change" represents participants' readiness to reduce cannabis use which is based on a measure adapted from the readiness ruler (26). "Days of Use" represents the number of days of cannabis use in the past month. Instances of superscribed "a" denote statistically significant differences ($p < 0.05$) between ESI-c and ESI groups for the variable in question.

Event Retrieval

To assess the retrieval of events, participants were prompted using Episodic Recent Thinking [ERT, (23, 24)]. Episodic Recent Thinking prompts episodic thinking of positive events from yesterday during 3-h intervals [(25), 4–7 p.m., 1–4 p.m., 10–1 p.m., 7–10 a.m. (23, 24)]. Participants typed short answers to six questions about the episodic details of each event (e.g., "What were you doing?," "Who were you with?," "What were you tasting and smelling?") to facilitate engaging in the rewarding and specific details of the events.

Measures

Demographics and Substance Use

Table 1 shows distributions and descriptive statistics for demographic variables and cannabis use measures. Participants ranged from age 19–75 ($M = 36.4$ years, $SD = 10.8$), and 49% were female. Most participants were college educated (52%) and were employed full-time (67%). All cannabis use measures regarding use during the 30 days before the ESI/ESI-c session were ordinal in nature. Median number of days of cannabis use was 10–19 days per month (IQR = 1–2, 26–29 days).

Approximately half of the total sample (52%) met criteria for a cutoff score on the Cannabis Use Disorder Identification Task-Short Form (CUDIT-SF), which has been shown to be predictive of a CUD diagnosis (27). Participants answered the question, "How important is it for you to reduce your cannabis use?" using an 11-point visual analog scale (VAS) with anchors of "not" important at 0 and "very" important at 10. This assessment was adapted from the readiness ruler and was assessed pre and post-intervention (26). Participants averaged 2.3 on readiness to change cannabis use prior to the ESI/ESI-c intervention ($SD = 2.5$).

Specificity and Reward Ratings

For every event generated during ESI or ESI-c sessions, participants rated the excitement, enjoyment, and importance (i.e., how rewarding) and the vividness (i.e., specificity) on separate 100-point VASs. These ratings were considered a measure of engagement for each event (23). To create an average engagement score, all four engagement ratings were averaged for each participant.

Analysis Plan

To examine potential differences in subjective episodic memory measures based on frequency of cannabis use responses on frequency of cannabis use days in the past month (i.e., 1–2, 3–5, 6–9, 10–19, 20–25, 26–29, all 30 days) were dichotomized into low to moderate frequency use (1–25 days; Low to Moderate Frequency Group) and more frequent use (26–30 days; High Frequency Group). These specific cutoff points for frequency of cannabis use were chosen in part because the median response ranged between 26 and 30 days of use in prior studies (17, 28). Further, because the modal response in the current study was 26–29 days of use, which was selected twice as frequently as the 20–25 days option, and the 10–19 days option was the least frequently selected option, the cut-off point of 26 days appeared to be the most data-based cutoff for this sample.

Demographic variables and cannabis-related variables were compared between ESI and ESI-c groups using chi-squared tests (categorical variables) and one-way ANOVAs (continuous variables). Those in the ESI condition were significantly older and were less likely to be employed full-time. No significant differences were observed between the two conditions on gender, education, the sum of the CUDIT-SF score, or readiness to change cannabis use. Age, employment, CUDIT-SF summed score, and gender were included as covariates in the main models of this study because age and employment differed between the two conditions and because both gender and problematic cannabis use have been consistently associated with deficits in episodic memory in past studies.

Four separate two-way ANCOVAs (ESI condition x frequency of use group) controlling for age, employment, CUDIT-SF summed score, and gender were performed to test for differences in specificity (vividness) and reward ratings (enjoyment, excitement, and importance) during ERT. ANCOVAs were used instead of a single MANOVA because each of the four dependent measures were highly correlated ($rs = 0.54$–0.77), which suggests the need to test for differences in separate models to avoid potential type I error.

RESULTS

Figure 1 details the results in adjusted means from two-way ANCOVAs for each event rating. For vividness ratings (specificity), there was a significant main effect of condition found such that those in the ESI condition demonstrated greater vividness ratings than those in the ESI-c condition [$F_{(1, 125)} = 11.35$, $p < 0.01$, $d = 0.60$]. There was a significant main effect of frequency found such that those in the high frequency group showed lower vividness ratings relative to the low to moderate frequency group [$F_{(1, 125)} = 4.57$, $p < 0.05$, $d = 0.38$]. A significant interaction effect for condition was not observed [$F_{(1, 125)} = 0.80$, $p = 0.37$, $d = 0.16$]. These findings suggest that ESI was associated with enhanced vividness ratings relative to ESI-c, that those in the high frequency cannabis use group showed lower vividness ratings than the low to moderate frequency group, but that ESI was not significantly more effective at enhancing vividness in high relative to low to moderate frequency cannabis use groups.

For the excitement ratings (reward), results of the two-way ANCOVA revealed greater ratings for those in the ESI than in the ESI-c condition [$F_{(1, 125)} = 8.99$, $p < 0.01$, $d = 0.54$] and lower ratings for those in the high frequency relative to low to moderate frequency group [$F_{(1, 125)} = 5.45$, $p < 0.05$, $d = 0.42$]. There was not a significant interaction between ESI and frequency of cannabis conditions [$F_{(1, 125)} = 0.72$, $p = 0.40$, $d = 0.16$]. These findings suggest that ESI was associated with enhanced excitement ratings relative to ESI-c, that those in the high frequency cannabis use group showed lower excitement ratings than those in the low to moderate frequency group, and that ESI was not significantly more effective at enhancing excitement in high relative to low to moderate frequency cannabis use groups.

For the importance ratings (reward), results of the two-way ANCOVA revealed greater ratings for those in the ESI condition than in the ESI-c condition [$F_{(1, 125)} = 5.76$, $p < 0.05$, $d = 0.43$], but there was not a significant difference in importance between those in the high frequency and low to moderate frequency groups [$F_{(1, 125)} = 0.80$, $p = 0.37$, $d = 0.16$] or a significant interaction [$F_{(1, 125)} = 0.89$, $p = 0.35$, $d = 0.17$]. These findings suggest that ESI was associated with enhanced importance ratings relative to ESI-c, that frequency of cannabis use was not associated with importance ratings, and that ESI was not significantly more effective at enhancing importance in the high relative to the low to moderate frequency cannabis use groups.

For the enjoyment ratings (reward), results of the two-way ANCOVA revealed that there were not any significant differences between ESI and ESI-c conditions [$F_{(1, 125)} = 1.87$, $p = 0.17$, $d = 0.25$], between those in the high frequency and low to moderate frequency groups [$F_{(1, 125)} = 1.35$, $p = 0.25$, $d = 0.21$] or a significant interaction [$F_{(1, 125)} = 0.0001$, $p = 0.99$, $d = 0.00$]. Due to the lack of a significant main effect or interaction effect, no follow-up ANCOVA models were performed. These findings suggest that enjoyment ratings were not associated with frequency of cannabis use, were not enhanced by ESI, and were not differentially augmented in those who reported high relative to low to moderate frequency cannabis use.

DISCUSSION

This study examined whether more frequent cannabis use is associated with deficits in subjective episodic memory (i.e., specificity and reward retrieval ratings), and whether an ESI intervention could enhance subjective episodic memory relative to an ESI control condition. We observed lower ratings in high frequency users for vividness and excitement relative to the low to

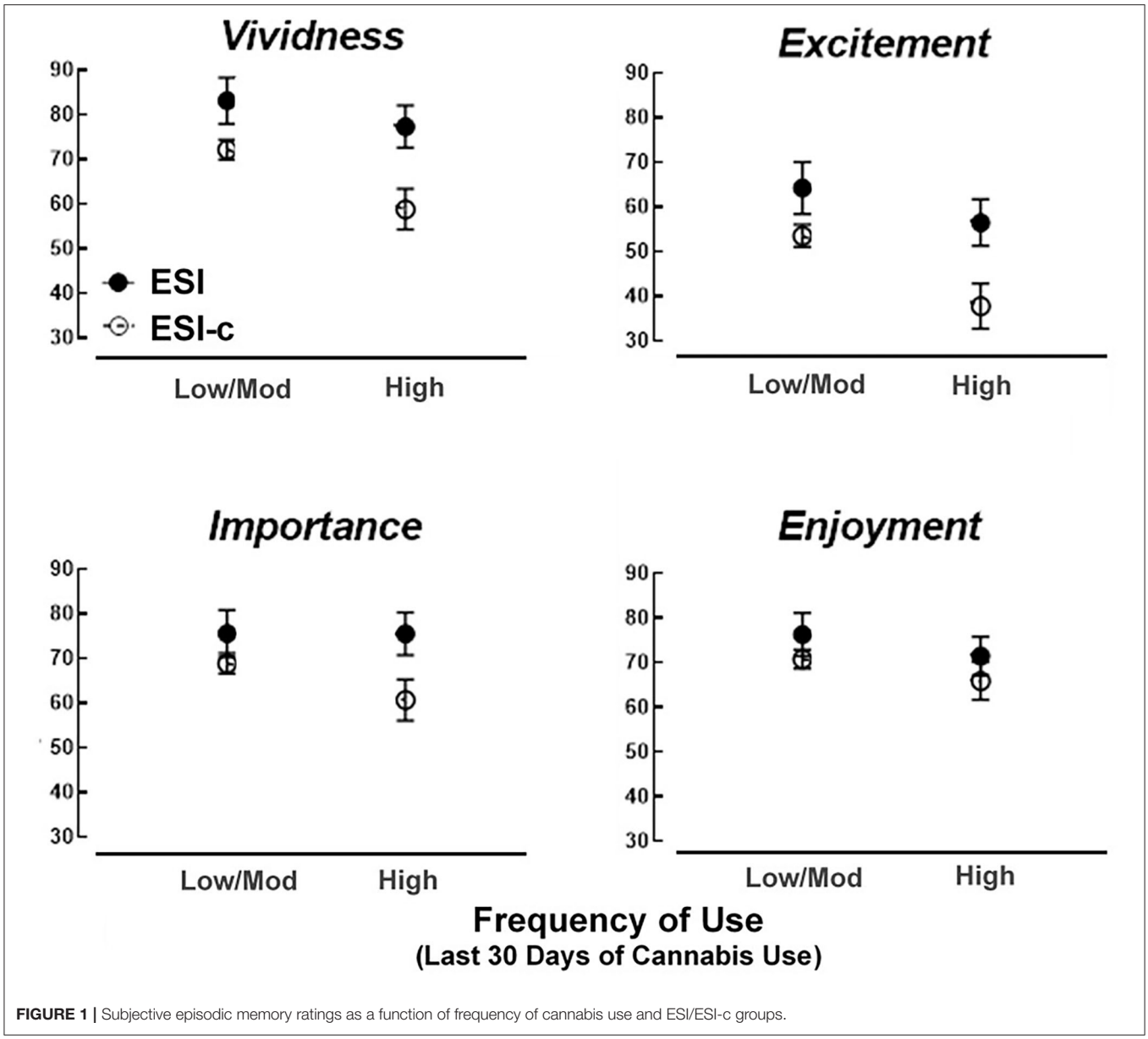

FIGURE 1 | Subjective episodic memory ratings as a function of frequency of cannabis use and ESI/ESI-c groups.

moderate frequency users, which would be suggestive of deficits associated with more frequent cannabis use. Those receiving the ESI intervention showed greater vividness, excitement, and importance ratings relative to those who received the ESI-c intervention, which suggests that the ESI may improve subjective measures of episodic memory among cannabis users. Importantly, no significant interaction effects between ESI condition and frequency of cannabis use groups were found, which suggests that the subjective episodic memory measures were not enhanced by ESI to a greater extent in high frequency relative to low to moderate frequency cannabis users in this study. One interpretation of the current findings is that specificity (vividness) of event recall may be impacted to a greater extent by frequent cannabis use than by how rewarding recalled events are perceived to be, thus providing a potentially more relevant treatment target for interventions designed to reduce cannabis use. Such an interpretation would be congruent with evidence suggesting that episodic memory deficits are more pronounced than reward-related deficits among regular cannabis users (10).

The failure to observe a consistent effect of cannabis use frequency and ESI condition across all four reward ratings was unexpected given that more specific event recall often corresponds with more positive perceptions of past and potential future events (20). One potential reason for this finding is the current study prompted recall of events from the prior day, in contrast to other studies which have provided a broader time frame for participants to choose (29). Thus, there may have been less variability in the reward ratings in this study because there was a more restricted opportunity to recall past positive events. Although reward and specificity of event recall have

been significantly related to each other in prior studies, there is also some evidence suggesting that the two constructs are bidirectionally related (4). Thus, it may be necessary to also target valuation of retrieved events to enhance cognitive processes such as DD and emotional regulation by prompting the elaboration of positive and rewarding features of the video events presented by the ESI.

This study is the first to our knowledge to demonstrate the initial efficacy of a brief intervention to improve engagement in episodic retrieval in frequent cannabis users. The current digital version of ESI was completed in 10 min on average, which suggests the feasibility of administering the ESI in real-world environments. Our findings are congruent with other brief intervention studies that observed improvement in specificity of events among those with Major Depressive Disorder and Schizophrenia (6, 30). Of potential importance to the health behavior treatment field, is to determine if ESI can improve engagement in Episodic Future Thinking (EFT), a brief intervention currently being tested for reducing nicotine, alcohol, and cannabis use and improving healthy food choices (22–24, 31). Episodic Future Thinking is an intervention that prompts participants to create and imagine positive, personally relevant future events and is thought to be a product of episodic memory processes and the ability to focus on the future (18, 32). Through strengthening episodic memory processes, administering ESI prior to EFT may improve engagement in EFT, thus improving DD and potentially increasing the impact on reductions in cannabis use and other substances (22).

Several limitations of this study warrant note. Data from the ESI-c and ESI were derived from two separate studies and participants were recruited through two separate online mechanisms (i.e., Mechanical Turk and Qualtrics Panels), which may have influenced the findings due to variations in the sample characteristics between the two recruitment sources. The impact of this sampling strategy was minimized as the studies used the same experimental conditions and similar inclusion criteria and all variables that were significantly different between the two conditions were controlled for in analyses. The modest sample size posed another limitation. Statistical power was not optimal and raises concern about the reliability and generality of the findings, particularly in relation to the lack of significant interactions between ESI condition and frequency groups observed. Future studies that recruit larger samples and randomize participants to roughly equivalent group sizes appear warranted. Approximately half of the participants in this sample met criteria cutoff scores for CUD using a validated screening tool; however, they were not formally diagnosed with CUD, and so the relevance of CUD in the context of the current study should be further explored in a clinical CUD sample. Also, participants in the current study reported relatively high frequency cannabis use patterns and the clinical validity of the specific cutoff point used (i.e., <26 days, 26–30 days) has not been empirically established. Even in the low to moderate frequency cannabis group, participants could have used 5 days a week, which may limit the generality of these findings to individuals who use cannabis less frequently.

Despite these limitations, our findings suggest that subjective episodic memory deficits should continue to be explored as a potentially important marker of cognitive vulnerability. If such deficits are indeed ubiquitous with frequent and problematic cannabis use, they may provide new treatment targets for CUD interventions and potentially help inform the development of novel treatment approaches.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Dartmouth Committee for the Protection of Human Subjects. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MS and AB performed study conceptualization and design. MS performed data collection and analysis. SL performed programming of study methods and analysis. MS and AB performed writing and SL performed editing. All authors contributed to the article and approved the submitted version.

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Early, Chronic, and Acute Cannabis Exposure and Their Relationship With Cognitive and Behavioral Harms

Hugo López-Pelayo[1,2†], Eugènia Campeny[1†], Clara Oliveras[1,2], Jürgen Rehm[3,4,5,6], Jakob Manthey[7,8,9], Antoni Gual[1,2‡] and Maria de las Mercedes Balcells-Olivero[1,2‡]*

[1] Grup Recerca en Addiccions Clínic (GRAC), Institut de Recerca Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, Spain, [2] Psychiatry Department, Neuroscience Institute, Hospital Clínic de Barcelona, Barcelona, Spain, [3] Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada, [4] Department of Psychiatry, Dalla Lana School of Public Health, University of Toronto (UofT), Toronto, ON, Canada, [5] Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden, Germany, [6] Department of International Health Projects, Institute for Leadership and Health Management, I.M. Sechenov First Moscow State Medical University, Moscow, Russia, [7] Faculty of Psychology, Institute of Clinical Psychology and Psychotherapy, Technical University Dresden, Dresden, Germany, [8] Department of Psychiatry and Psychotherapy, Center for Interdisciplinary Addiction Research of Hamburg University (ZIS), University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany, [9] Department of Psychiatry, Medical Faculty, University of Leipzig, Leipzig, Germany

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Daniel Feingold, Ariel University, Israel

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****Correspondence:***
Eugènia Campeny
campeny@clinic.cat

[†]These authors share first authorship

[‡]These authors share senior authorship

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Background: Cannabis is the third most consumed drug worldwide. Thus, healthcare providers should be able to identify users who are in need for an intervention. This study aims to explore the relationship of acute, chronic, and early exposure (AE, CE, and EE) to cannabis with cognitive and behavioral harms (CBH), as a first step toward defining risky cannabis use criteria.

Methods: Adults living in Spain who used cannabis at least once during the last year answered an online survey about cannabis use and health-related harms. Cannabis use was assessed in five dimensions: quantity on use days during the last 30 days (AE), frequency of use in the last month (AE), years of regular use (YRCU) (CE), age of first use (AOf) (EE), and age of onset of regular use (AOr) (EE). CBH indicators included validated instruments and custom-made items. Pearson correlations were calculated for continuous variables, and Student's *t*-tests for independent samples were calculated for categorical variables. Effect sizes were calculated for each of the five dimensions of use (Cohen's *d* or *r* Pearson correlation) and harm outcome. Classification and Regression Trees (CART) analyses were performed for those dependent variables (harms) significantly associated with at least two dimensions of cannabis use patterns. Lastly, logistic binary analyses were conducted for each harm outcome.

Results: The mean age of participants was 26.2 years old [standard deviation (SD) 8.5]. Out of 2,124 respondents, 1,606 (75.6%) reported at least one harm outcome (mean 1.8 and SD 1.5). In our sample, using cannabis on 3 out of 4 days was associated with an 8-fold probability of scoring 4+ on the Severity Dependence Scale (OR 8.33, 95% CI 4.91–14.16, $p < 0.001$), which is indicative of a cannabis use disorder. Also, a start of regular cannabis use before the age of 25 combined with using cannabis at least once per month was associated with a higher probability of risky alcohol use (OR 1.33, 95% CI 1.12–1.57, $p = 0.001$). Besides, a start of regular cannabis use before the age of

18 combined with a period of regular use of at least 7.5 years was associated with a higher probability of reporting a motor vehicle accident (OR 1.81, 95% CI 1.41–2.32, $p < 0.0001$). Results were ambiguous regarding the role that age of first use and milligrams of THC per day of use might play regarding cannabis-related harms.

Conclusions: The relationship among AE, CE, and EE with CBH indicators is a complex phenomenon that deserves further studies. The pattern of cannabis use should be carefully and widely evaluated—(not just including frequency but also other dimensions of pattern of use)—in research (preferably in longitudinal studies) to assess cannabis-related harms.

Keywords: Cannabis, cognition, behavior, health, harm, THC, risk

BACKGROUND

Cannabis is the third most prevalent psychoactive substance used worldwide. Globally, there were an estimated 192 million past-year users of cannabis in 2018, corresponding to 3.9% of the global population aged 15–64 (1). In Europe, 90.2 million adults (aged 15–64), or 27.4% of this age group, reported lifetime cannabis use. Among this whole group, 7.6% reported use during the last year. The prevalence of last year use was higher (15.0%) among the younger ones (aged 15–34) (2).

Cannabis legislative frameworks are evolving worldwide (3, 4), and global tendencies point out that cannabis use is increasing, while the perception of risks associated to cannabis is declining (5). Previous literature has extensively documented multiple health-related harms associated with cannabis use. Besides several somatic harms such as respiratory adverse events, cancer, cardiovascular outcomes, and gastrointestinal disorders, the deleterious consequences of cannabis use on mental health, cognition, and behavior are well-documented (6, 7).

Regarding mental health, multiple studies have revealed a clear relationship between cannabis consumption, and both psychotic symptoms (8) and risk for developing schizophrenia, especially among heavy cannabis users, compared to non-users (9). Cannabis use has an impact on incidence of psychotic experiences (10). Moreover, age at onset of psychosis is on average 2.7 years earlier for cannabis users (11). Also, several studies have suggested that cannabis consumption may represent a risk factor for depression (12), mainly after long-term and heavy use (13). Cannabis use has also been associated with bipolar disorder (14) and the development of anxiety symptoms in the general population (15). Lastly, cannabis users may also develop a cannabis use disorder (16, 17). Using cannabis both daily and weekly, early onset of use (11–15 years) and the experience of positive psychotropic effects of cannabis are considered risk factors for onset of cannabis use disorders (18).

Additionally, there is enough evidence to endorse the claim of a negative impact of chronic cannabis use on cognition (19, 20), even after the person is no longer acutely intoxicated ("stoned") by cannabis use. Memory is the most consistently impaired cognitive domain (21). Verbal learning and memory tasks seem to be distinctly sensitive to both the acute and chronic effects of cannabis, with mixed evidence regarding improvement with abstinence. Working memory seems to be affected by acute cannabis use and also by chronic use, mostly in young and adolescent users, but appears to mostly resolve with prolonged periods of abstinence. Although, impaired attention has often been considered an indication of the intoxicating effects of cannabis, there is evidence for both acute and chronic exposure impairing this cognitive domain. Psychomotor function is affected by acute intoxication and this likely persists for some time following chronic cannabis exposure. Regarding executive functions, there are clear acutely impairing effects on inhibition, whereas, planning, problem solving, reasoning and interference control may be more affected in older chronic users, or with greater exposure to cannabis. Risky decision making and sensitivity to reward are increased during acute intoxication but the extent to which these effects persist in chronic or abstinent users remains unclear (22). Chronic cannabis use also alters concentration (23).

Cannabis use also seems to be a risk factor for negative behavioral outcomes (24) such as suicidal behavior, violence, and motor vehicle accidents (25).

Up to this moment, there is insufficient evidence on what exactly risky use constitutes, making it difficult for healthcare providers to identify users who qualify for an intervention.

Previous studies usually focus on one single harm (e.g., anxiety) and one single dimension of pattern of cannabis use (e.g., frequency of use). Using the data obtained in a survey that was answered by a sample of 2,124 Spanish adult cannabis users, mostly men in their 20's with university degrees, we aim to explore the relationship among five dimensions of cannabis use (quantity, frequency, years of regular use, age of onset, and age of initiation regular use)—grouped as acute exposure (quantity and frequency of use), early exposure (age of onset and age of initiation of regular use), and chronic exposure (years of regular use)—and 12 indicators of cognitive and behavioral related harms.

Although the cross-sectional design of our study will not allow to establish causality or to assuredly define the cutoff point for frequency, quantity, age of first use, age of initiation of regular

Abbreviations: AOf, Age of onset (first use of cannabis); AOr, Age of onset (regular cannabis use); CUD, Cannabis use disorder; DU, Days of cannabis use during the previous 30 days; YRCU, Years of regular use.

use, or years of regular use that affect harm, our results will increase the evidence in favor of considering not just frequency of use but also other dimensions of cannabis use in both research and clinical practice.

MATERIALS AND METHODS

Design, Setting, and Procedure of the Study

The flow process is outlined in **Figure 1**. From March 2019 to February 2020, a sample of 2,124 people was recruited for a cross-sectional study. Adults (≥18 years old), living in Spain, who used cannabis at least once during the last 12 months were eligible to participate. Exclusion criteria were as follows: (a) no reported data about patterns of cannabis use; (b) idiomatic barriers (cannot understand Spanish); (c) incapacity to sign the informed consent; and (d) no access to the Internet. Outliers for two variables (milligrams THC per day of use during the last month and sum of harms) were excluded if Z-score $\pm$ 2.5 (deviation from mean).

An online survey was distributed among different organizations, which have access to people who use cannabis. They provided the link to access the survey about their internal networks. Five universities (including students associations), one federation of cannabis users association, seven media webs, eight researchers, and 13 other social and scientific organizations participated in the distribution.

The survey in itself was anonymous. However, upon completion of the survey, participants were given the opportunity to participate in a raffle of 10 vouchers for exchanging in a website of travels and gifts (138€ each voucher). The data collected as part of the raffle were not combined with survey responses at any time.

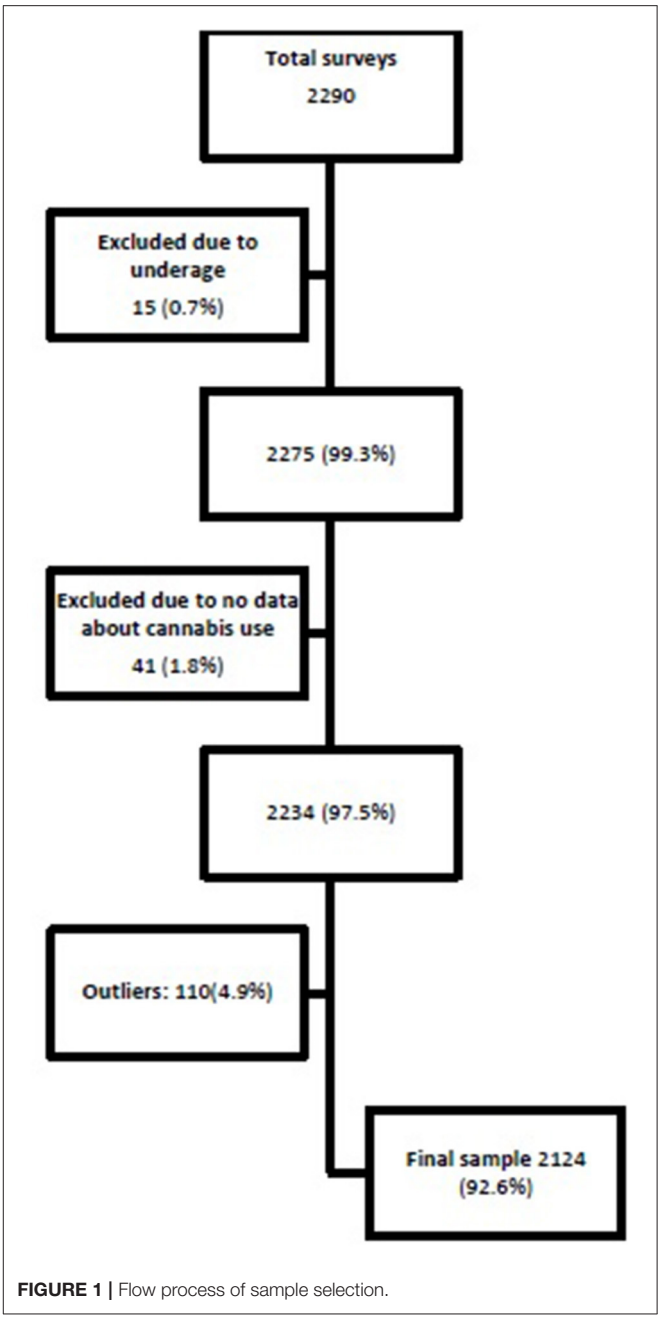

FIGURE 1 | Flow process of sample selection.

Assessment

An online survey was designed based on a recent systematic review of systematic reviews about cannabis-related harm (7). The survey was tested through a pilot study (under review).

The survey included 55 questions (for more details, see **Supplementary Materials**), divided into four sections.

1) Socio-demographic characteristics (age, gender, education, marital status, and working status).
2) Substance use during the last 12 months (tobacco, alcohol, cocaine, opioids, amphetamines, LSD, and benzodiazepines without prescription); alcohol use was measured through the Alcohol Use Disorder Identification Test—C (AUDIT-C) (26).
3) Patterns of cannabis use, type of cannabis derivate use (herbal, hash, herbal and hash, other), administration route (smoked, ingested, vaping, other), frequency of use (number of days of use during the last month), age at first use and age of regular use onset (patients' self-perception), years of regular use (assessed according to years between age at regular use and current age), milligrams of delta-9-THC per day of use during the last month based on the Standard Joint Unit (quantity assessed according to the following equivalences: 7 mg delta-9-THC = 1 joint = 250 milligrams cannabis per joint = 1€) (27), and site of purchase (cannabis association, own production, dealer, friends, other or several ways).
4) Health status and injury background. The following scales were included in the survey for assessing psychological harms (found in the systematic review of the literature): (a) Severity Dependence Scale (SDS) for cannabis use (28); (b) General Anxiety Disorder-7 (GAD-7) (29); (c) Patient Health Questionnaire-9 (PHQ-9) (30); (d) Multicage CAD-4 for gaming (CAD-4) (31). Other harms were explored with (e) Sleep problems based on questions 2110–2111 of "World Health Organization Survey about health and health system

responsiveness" (32) and (f) Cognitive impairment based on questions of the first domain (cognition) of "WHODAS 2.0. Measuring health and disability: manual for WHO disability assessment schedule" (33) that are also used in "World Health Organization Survey about health and health system responsiveness" (32): "In the past 30 days, how much difficulty did you have in: Concentrating on doing something for 10 min?, Remembering to do important things?, Analyzing and finding solutions to problems in day-to-day life?, Learning a new task, for example, learning how to get to a new place?"; (g) *Ad hoc* questions about violence: "Have you ever experienced any of the following situations in your family? (verbal violence and physical violence) Who perpetrated the violence?" (positive outcome was considered only if the user perpetrated physical violence); (h) *Ad hoc* questions about motor vehicle accidents: "Have you ever experienced a motor vehicle accident? Have you consumed cannabis the 6 h before the collision?" (positive outcome was considered only if positive answer to both questions) (7); (i) *Ad hoc* questions about mental health "Have you ever been diagnosed with any of the following illness? Depressive disorder; Anxiety disorder; Bipolar disorder; Other, specify; No, never"; (j) *Ad hoc* questions about suicidal impulses: "Have you ever thought of hurting yourself? Have you ever attempted?" (positive outcome was considered if affirmative response to at least one question); (k) *Ad hoc* questions about previous treatment for drug use disorders: "Have you ever been in treatment for any of the following substances? Alcohol; Cocaine; Cannabis; Heroin; Other, specify; No, never."

Statistical Analyses

A descriptive analysis of qualitative variables was conducted using frequencies and percentages. Mean and standard deviation (SD) were used for continuous variables.

Dependent Variables

Total score SDS, total score GAD-7, total score PHQ-9, total score CAD-4, and total score AUDIT-C. Two categories according to previous treatment for drug use disorder (no and yes), two categories for suicidal impulses (no and thoughts or attempts), two categories for mental health (no previous mental health diagnosis and previous mental health diagnosis), two categories for motor vehicle accidents (no or yes and cannabis use 6 h before collision), two categories for experience of violence (no and yes), two categories for cognitive impairment (no and yes), and two categories for sleep disorders (no and yes). Only for calculating the number of harms for each respondent was a cutoff established for SDS (>4), GAD7 (>4), PHQ-9 (>4), CAD-4 (>1), and AUDIT-C (>4).

Independent Variables

Milligrams THC per day of use during the last 30 days (measure of acute exposure), days of use during the last 30 days (DU) (measure of acute exposure), age of cannabis onset (AOf) (first use) (measure of early exposure), age of regular cannabis onset (AOr) (measure of early exposure), and years of regular use *(YRCU)* (measure of chronic exposure).

Univariate parametric tests were performed using Student's *t*-test for independent samples for categorical variables as independent and Pearson correlation tests for continuous variables. Standardized effect sizes (Cohen's *d*) were calculated for statistically significant associations (p-value <0.05). For correlations, $r < 0.10$ was not interpreted, r between 0.10 and under 0.30 was considered a small effect size, r from 0.30 and under 0.50 was considered a medium effect size, and r value $\geq$ 0.50 was considered a large effect size. Cohen's d values were calculated; values under 0.20 were not interpreted, those between 0.20 and under 0.50 were considered small effect size, those between 0.50 and under 0.80 were considered medium, and those $\geq$0.80 were considered large effect size (34).

Since we aimed to explore the relationship between different dimensions of cannabis use patterns internally and with self-reported cannabis-related harms on a successive phase of exploration, we performed Classification and Regression Trees (CART) analyses for those dependent variables (harms) significantly associated with at least two dimensions of cannabis use patterns (independent). CART analyses are used as an exploration method to classify systems that differ due to natural causes, in our case patterns of cannabis use. CART analysis is a type of decision tree learning technique and, consequently, is useful for creating a predictive model. In our analyses, we used CART analyses to explore potential predictive models of cannabis-related harms based on patterns of cannabis use. As dependent variables, we included those harms with at least two dimensions of use patterns associated with a single harm in the univariate analyses, and as independent variables, we included those patterns of use associated with this specific variable. Based on the association of cannabis use patterns and experience of cannabis-related harms, the CART analysis allows us to distinguish users experiencing harm from those not experiencing harm based on their use patterns. Lastly, logistic binary analyses were conducted for each harm outcome, in order to quantify the risk for those use patterns identified in CART analyses to be predictive in classifying homogeneous user groups. These analyses were adjusted for age, gender, tobacco use, and other illegal drug use.

All statistical analyses were performed with SPSS statistical package version 20.0© and Microsoft Office Excel 2007©.

Ethics

The protocol was approved by the Ethics Committee of Hospital Clínic de Barcelona (HCB/2017/0795) according to the Helsinki Declaration (update Fortaleza 2013) and the national regulations.

RESULTS

Descriptive Analyses

A total of 2,124 people who had used cannabis during the previous year answered the online survey and provided sufficient data regarding their cannabis use to be included in the analyses (see **Figure 1**); 68.6% were men, the mean age was 26.2 years old (SD 8.5), 58.1% were employed, and 51.6% had completed a university degree. Also, 75.6% reported at least one harm associated with chronic cannabis use in the literature. Type

TABLE 1 | Socio-demographic and cannabis use characteristics of the sample.

Categorical variables	*N* (%)
Gender	
• Males	1,457 (68.6)
• Females	652 (30.7)
• Other	15 (0.7)
Working status	
• Student	754 (35.8)
• Employment out of home	1,224 (58.1)
• Employment at home	32 (1.5)
• Unemployment	67 (3.2)
• Retired	22 (1.0)
• Leave	5 (0.2)
• Other	3 (0.1)
Studies	
• No studies	2 (0.1)
• Primary	34 (1.6)
• Secondary	969 (46.7)
• University	1071 (51.6)
Marital status	
• Single	13,232 (62.9)
• Couple	732 (34.8)
• Divorced	48 (2.3)
• Widow	2 (0.1)
Type of cannabis	
• Mainly Hash	311 (16.0)
• Mainly Herbal	1,241 (62.4)
• Both equally	407 (20.9)
• Other	14 (0.7)
RoA	
• Smoked	1,933 (96.3)
• Ingested	38 (1.9)
• Vaped	30 (1.5)
• Several routes or other routes	7 (0.3)
Purchase	
• Cannabis club	618 (30.0)
• Own production	227 (11.0)
• Dealer	554 (26.9)
• Friends	656 (31.8)
• Other/several ways	8 (0.4)
Cannabis use last 30 days	
• 0 days	453 (21.4)
• 1–19 days	783 (37.0)
• 20 or + days	879 (41.6)
Years regular cannabis use	
• 0–1	309 (18.6)
• 2–10	923 (55.7)
• >10	425 (25.6)
Mg THC per day (last month)	
• 0	462 (21.8)
• 1–6	58 (2.7)
• 7–14	975 (45.9)
• 15–21	264 (12.4)
• >21	365 (17.2)
Continuous variables	**Mean** / **SD**
Age	26.2 / 8.5
Age onset first use (cannabis)	16.6 / 2.7
Age onset regular use (cannabis)	19.9 / 4.4
Years of regular use	7.7 / 7.9
Mg per day (according to Standard Joint Unit	13.6 / 14.1
Cognitive and behavioral problems	1.8 / 1.5

(Continued)

TABLE 2 | Prevalence of other drug use in the sample.

Drug use	*N* (%)
Tobacco use	847 (39.9)
Illegal drugs (lifetime)	1,142 (53.8)
Cocaine	
- Past	355 (16.7)
- Current	353 (16.6)
Opioids	
- Past	120 (5.6)
- Current	45 (2.1)
Amphetamine	
- Past	354 (16.7)
- Current	496 (23.4)
LSD	
- Past	302 (14.2)
- Current	162 (7.6)
Non-prescribed BZD	
- Past	147 (6.9)
- Current	124 (5.8)

of cannabis used was often herbal (62.4%) and the route of administration was mainly smoked (96.3%). In our sample, 774 individuals (36.4% of the whole sample) reported risky alcohol use according to AUDIT-C (score >4); also, according to AUDIT-C, 63.7% of the sample reported use of alcohol at least twice a month. For more details about socio-demographic characteristics, patterns of cannabis use, and prevalence of other drug use, see **Tables 1**, **2**.

Univariate Analyses

Obtained data are described below, divided into the five independent variables: (1) milligrams THC per day of use during the last 30 days; (2) days of use during the last 30 days; (3) age of cannabis onset (first use); (4) age of regular cannabis onset; and (5) years of regular use. For more details, see **Tables 3**, **4**.

Violence, gambling, sleep disorders, cognitive impairment, suicidal impulses, anxiety, and depression were not associated with any independent variable.

TABLE 3 | Patterns of cannabis use and harm correlations.

Independent variables	SDS	AUDIT-C	PHQ-9	GAD-7	CAD-4
Mg THC per day last month	0.394*	0.066**	−0.02	−0.038	0.011
Days of use last month	0.523*	0.070***	−0.42	−0.66	0.004
Age of onset use	−0.145****	−0.134*	0.024	0.044	−0.051
Age of onset regular use	−0.102*****	−0.121*	0.012	−0.015	−0.093
Years of cannabis use	0.082	−0.050#	−0.095##	−0.040	0.099###

*Pearson correlation test, only statistically significant (<0.05): *p < 0.001; **p = 0.004; ***p = 0.02; ****p = 0.001; *****p = 0.037; #p = 0.049; ##p = 0.008; ###p = 0.038.*

Acute Exposure Measured by Milligrams Delta-9-THC per Day of Use During the Last Month

Mg of THC correlated with SDS score ($r = 0.394$; $p < 0.001$) and AUDIT-C score ($r = 0.066$; $p = 0.004$). The average daily intake of THC in the past 30 days was higher for those users who experienced a motor vehicle accident after cannabis use (<6 h) (13.2 vs. 17.0, $p = 0.01$; Cohen's $d = 0.26$) or received treatment for substance use disorder (SUD) (13.4 vs. 19.8, $p = 0.029$, Cohen's $d = 0.36$).

Acute Exposure Measured by Days of Cannabis Use During the Previous 30 Days

DU correlated with SDS score ($r = 0.523$; $p < 0.001$) and AUDIT-C score ($r = 0.070$; $p < 0.02$). Mean of days of use was higher for those users who experienced a motor vehicle accident after cannabis use (<6 h) (13.1 vs. 17.2, $p < 0.001$, Cohen's $d = 0.33$).

Early Exposure Measured by Age of Onset (First Use of Cannabis)

AOf correlated inversely with SDS score ($r = -0.145$, $p = 0.001$) and AUDIT-C score ($r = -0.134$; $p < 0.001$). The mean age of onset was lower for those users who had motor vehicle accidents (15.8 vs. 16.7, $p < 0.001$, Cohen's $d = 0.37$).

Early Exposure Measured by Age of Onset (Regular Cannabis Use)

AOr correlated inversely with SDS score ($r = -0.102$; $p = 0.037$) and AUDIT-C score ($r = -0.121$; $p < 0.001$). The mean age of onset of regular use was lower for those users who experienced motor vehicle accidents (19.7 vs. 18.1, $p < 0.001$, Cohen's $d = 0.44$). It was also lower for those users who reported history of mental health disorders (19.5 vs. 18.2, $p < 0.001$, Cohen's $d = 0.39$).

Chronic Exposure Measured by Years of Regular Use

YRCU correlated with CAD ($r = 0.099$; $p = 0.038$) and inversely with PHQ-9 ($r = -0.095$, $p = 0.008$) and AUDIT-C ($r = -0.050$, $p = 0.049$). The mean of years of regular use was higher for those users who had cognitive impairment (7.9 vs. 7.0, $p = 0.039$, Cohen's $d = 0.12$), experienced a motor vehicle accident after cannabis use (<6 h) (10.0 vs. 7.3, $p < 0.001$, Cohen's $d = 0.33$), or received treatment for SUD (13.2 vs. 7.4, $p < 0.001$, Cohen's $d = 0.66$).

Figure 2 provides a summary of results.

CART Analyses and Logistic Binary Regression Analyses

Harm 1: SDS Score > 4

In the CART analysis, we included those variables associated with SDS score > 4 in the univariate analysis (frequency of use, quantity of use, age of first use, and age of onset regular use).

According to the CART analysis, among survey respondents using cannabis >21 days in the last month, 46.9% had an SDS score > 4 (node 2, **Figure 3**), as compared to only 8.9% of those who used cannabis less frequently (node 1, **Figure 3**; whole sample: 23%). Other variables (quantity, age of first use, and age of onset regular use) did not explain additional variance.

After adjusting for age, gender, use of other illegal drugs, and tobacco use in a Logistic Binary Regression Analysis, those who used cannabis >21 days per month had eight times higher probability of SDS >4 (OR 8.33, 95% CI 4.91–14.16, $p < 0.001$).

Harm 2: AUDIT-C Score > 4, Suggestive of Risky Alcohol Use

In the CART analysis, we included those variables associated with AUDIT C > 4 (which is suggestive of risky alcohol use) in the univariate analysis (frequency of use, quantity of use, age of first use, and age of onset regular use).

According to the CART analysis, among survey respondents using cannabis at least 1 day in the last month and started using cannabis regularly before 25 years old, 44.6% had AUDIT-C positive (node 5, **Figure 4**), as compared with 39.6% of whole sample. Age of first use > 18.5 years old was associated with a lower risk of AUDIT-C > 4 in those who did not use cannabis in the last month (22.4%). Quantity of use did not explain additional variance.

After adjusting for age, gender, use of other illegal drugs, and tobacco use in Logistic Binary regression analyses, those who used cannabis at least once the last month had 1.5 times higher probability of AUDIT-C positive (OR 1.56, 95% CI 1.21–2.01, $p = 0.01$) while age of onset of regular use was not statistically significant in this model. However, a combination of both use indicators (regular use < 25 years and using cannabis at least once per month) was associated with increased risk of being AUDIT-C positive, as compared with those who had not any of them (OR 1.33, 95% CI 1.12–1.57, $p = 0.001$).

Harm 3: Motor Vehicle Accident < 6 h After Using Cannabis

In the CART analysis, we included those variables associated with motor vehicle accidents in the univariate analysis (frequency of

TABLE 4 | Cannabis use and harm categories univariate analyses.

		Mg THC (means, SD)	*t* (*p*)	Cohen's *d*	Day of use last month (mean, SD)	*t* (*p*)	Cohen's *d*	Age onset (mean, SD)	*t* (*p*)	Cohen's *d*	Age onset regular use (mean, SD)	*t* (*p*)	Cohen's *d*	Years of Cannabis use (mean, SD)	*t* (*p*)	Cohen's *d*
Sleep disorders	No	13.5 (13.9)	−1.029 (0.304)	N/A	13.7 (12.7)	1.380 (0.168)	N/A	16.5 (2.5)	−0.625 (0.532)	N/A	19.5 (4.2)	−0.094 (0.925)	N/A	7.6 (7.9)	0.687 (0.576)	N/A
	Yes	14.4 (15.4)			12.7 (12.9)			16.7 (3.7)		N/A	19.5 (5.5)		N/A	7.9 (8.4)		N/A
Mental health problems	No	13.5 (14.0)	−1.206 (0.234)	N/A	13.6 (12.7)	−0.429 (0.668)	N/A	16.6 (2.7)	0.626 (0.532)	N/A	19.5 (4.4)	<0.001	0.39	7.7 (7.9)	0.243 (0.808)	N/A
	Yes	16.8 (18.3)			14.4 (13.1)			16.3 (2.1)		N/A	18.2 (2.0)			7.3 (8.6)		N/A
Suicidal behavior	No	13.8 (14.1)	1.005 (0.315)	N/A	13.8 (12.7)	1.677 (0.094)	N/A	16.6 (2.5)	−0.863 (0.459)	N/A	19.5(4.4)	0.459 (0.687)	N/A	7.8 (7.9)	0.368 (0.226)	N/A
	Yes	13.0 (14.1)			12.6 (12.7)			16.7 (3.3)		N/A	19.3 (4.2)		N/A	7.2 (8.0)		N/A
Cognitive impairment	No	13.6 (14.1)	−0.410 (0.682)	N/A	13.4 (12.7)	−0.888 (0.374)	N/A	16.5 (2.5)	−0.442 (0.347)	N/A	19.6 (4.3)	1.134 (0.257)	N/A	7.9 (8.1)	2.070 (0.039)	0.12
	Yes	13.9 (14.1)			14.0 (12.8)			16.7 (3.3)		N/A	19.3 (4.6)		N/A	7.0 (7.5)		
Violence	No	13.6 (14.1)	−0.690 (0.490)	N/A	13.5 (12.7)	−1.047 (0.295)	N/A	16.6 (2.7)	0.375 (0.707)	N/A	19.5 (4.4)	0.171 (0.864)	N/A	7.6 (8.0)	−0.876 (0.381)	N/A
	Yes	14.8 (15.2)			15.1 (12.7)			16.4 (3.0)		N/A	19.4 (5.3)		N/A	8.5 (7.5)		N/A
Motor vehicle accidents	No	13.2 (13.9)	−3.514 (0.01)	0.26	13.1 (12.6)	−4.648 (<0.001)	0.33	16.7 (2.8)	5.948 (<0.001)	0.37	19.7 (4.6)	7.330 (<0.001)	0.44	7.3 (7.8)	−4.263 (<0.001)	0.33
	Yes	17.0 (15.7)			17.2 (12.6)			15.8 (2.0)			18.1 (2.7)			10.0 (8.3)		
Treatment for drug use	No	13.4 (13.8)	−2.247 (0.029)	0.36	13.5 (12.7)	−1.327 (0.185)	N/A	16.6 (2.7)	0.533 (0.596)	N/A	19.5 (4.3)	−0.269 (0.789)	N/A	7.4 (7.7)	−4.064 (<0.001)	0.66
	Yes	19.8 (20.4)			15.9 (13.6)			16.3 (3.5)			19.8 (7.1)			13.2 (10.0)		

t Student independent samples.

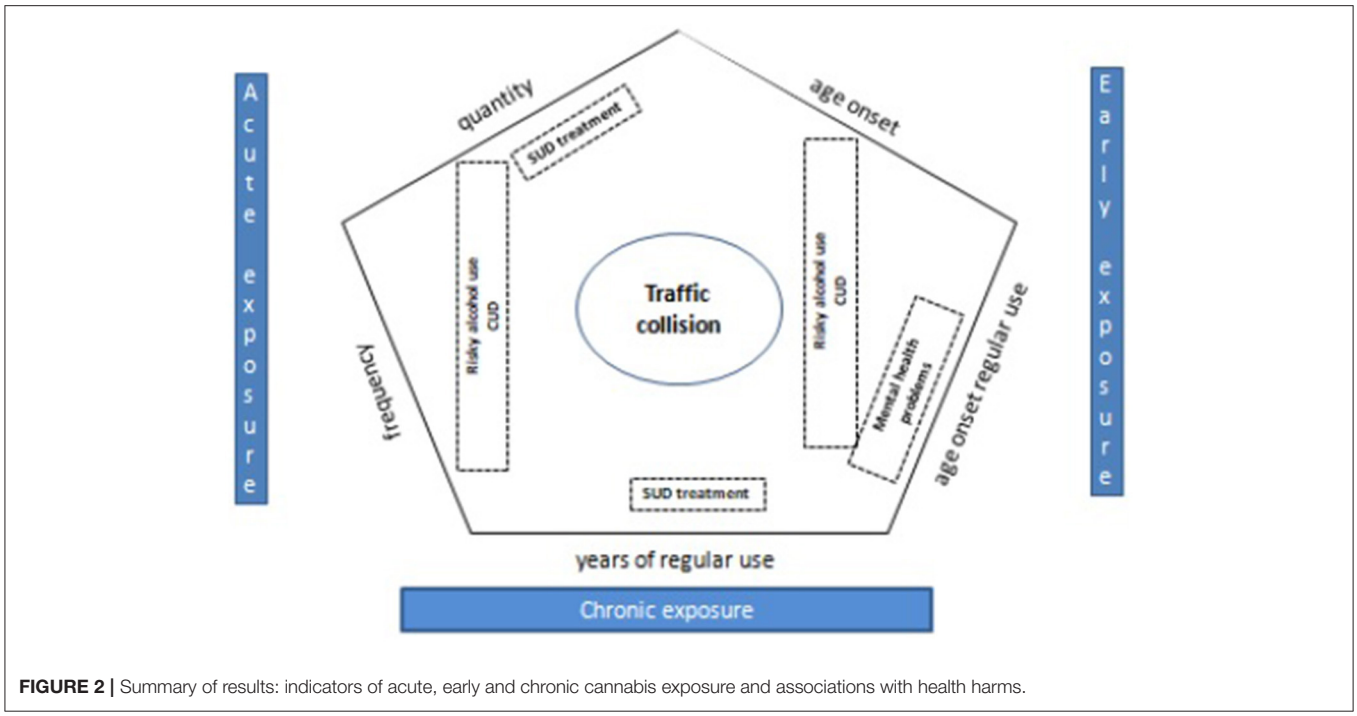

FIGURE 2 | Summary of results: indicators of acute, early and chronic cannabis exposure and associations with health harms.

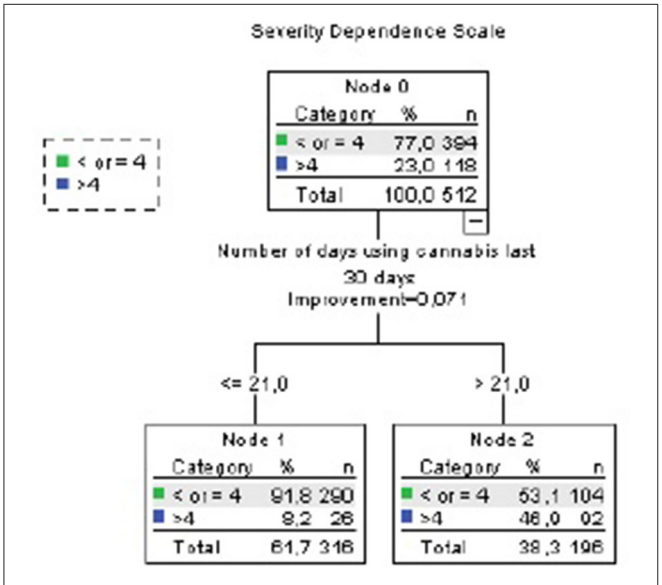

FIGURE 3 | CART analysis (Severity Dependence Scale). Accuracy 77%. Independent variables included: mg THC per day of use last month, days of use last month, age of first use, age of onset of regular use.

use, quantity of use, age of first use, age of onset regular use, and year of regular use).

According to the CART analysis, among survey respondents using cannabis for at least 7.5 years and initiated regular cannabis use before 18 years old, 23.6% had motor vehicle accidents (node 5, **Figure 5**), as compared with 3% of those who used cannabis <7.5 years and started cannabis use after 21.5 years old (node 4, **Figure 5**; whole sample: 10.8%). Other variables (quantity, frequency of use, and age of onset) did not explain additional variance.

After adjusting for age, gender, use of other illegal drugs and tobacco use in Logistic Binary regression analyses, those who use cannabis for at least 7.5 years had 1.4 times higher probability of motor vehicle accidents (OR 1.4, 95% CI 1.04–1.96, $p = 0.030$) and those who use cannabis regularly before 18 years old had 1.9 times higher probability of motor vehicle accidents (OR 1.93, 95% CI 1.43–2.60, $p < 0001$). Combination of both use indicators (regular use < 18 years and using cannabis at least during 7.5 years) was associated with higher probability of motor vehicle accidents (OR 1.81, 95% CI 1.41–2.32, $p < 0.0001$) compared with those who did not report these use patterns.

Harm 4: History of Treatment for SUDs

In the CART analysis, we included those variables associated with history of treatment for SUDs in the univariate analysis (frequency of use and year of regular use).

According to the CART analysis, among survey respondents using cannabis during at least 24.5 years, 14.3% had received treatment for SUDs (node 2, **Figure 6**), as compared with 1.1% of those who used cannabis during <6 years (node 3, **Figure 6**; whole sample: 2.5%). Quantity of use did not explain additional variance.

After adjusting for age, gender, use of other illegal drugs, and tobacco use in Logistic Binary regression analysis, years of regular use was not associated with treatment for SUDs.

Sensitivity Analyses (Those Who Reported Regular Use Since Before 18 Years Old; n = 517)

In these analyses, we did not include variables of age of onset of regular use because it was the selection criteria for this subsample.

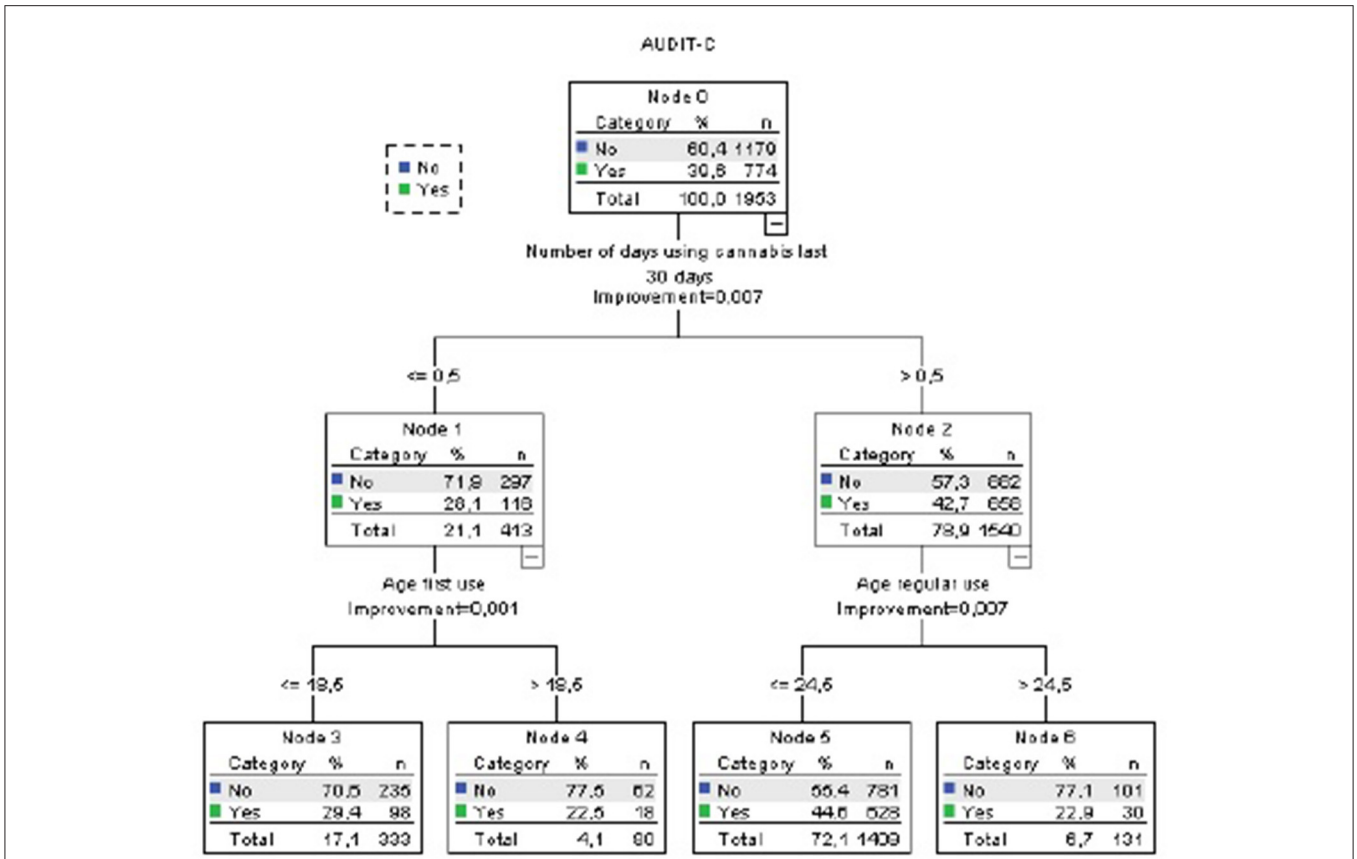

FIGURE 4 | CART analysis (Alcohol Use Disorder Identification Test-C). Accuracy 60.4%. Independent variables included: mg THC per day of use last month, days of use last month, age of first use, age of onset of regular use.

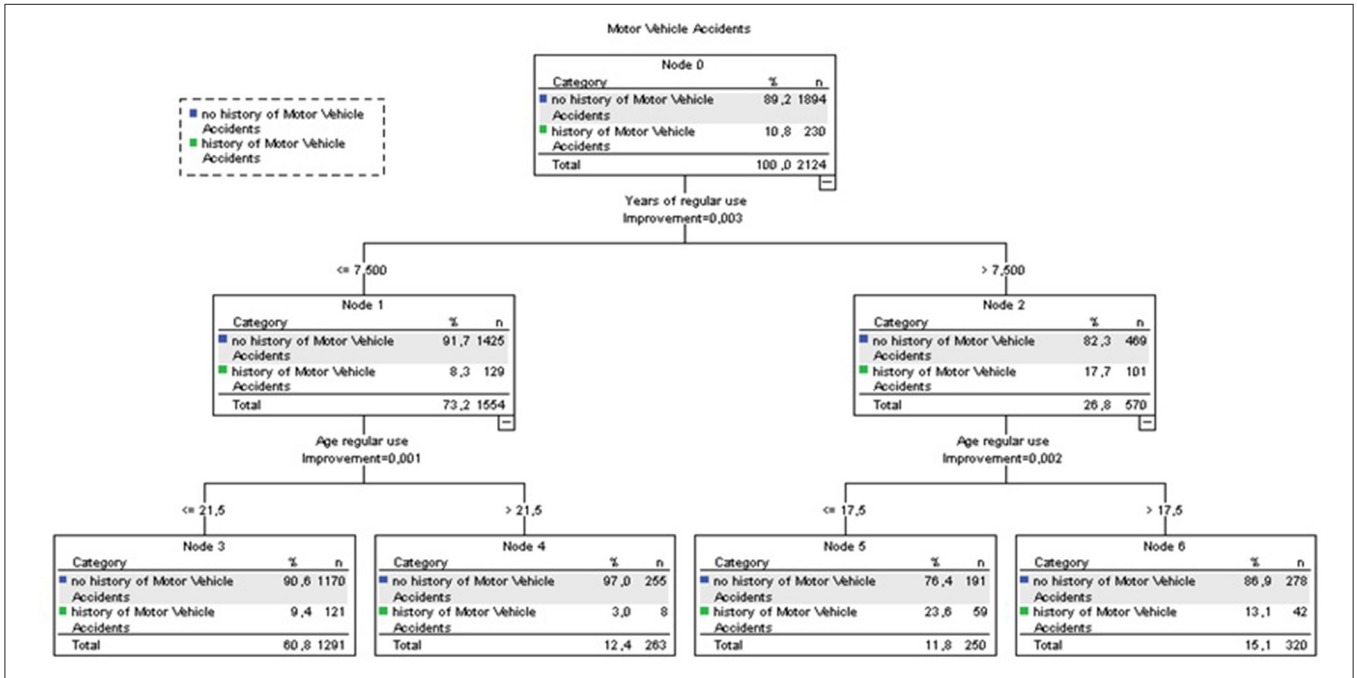

FIGURE 5 | CART analysis (Motor Vehicle Accidents). Accuracy 89.2%. Independent variables included: mg THC per day of use last month, days of use last month, age of first use, age of onset of regular use, years of regular use.

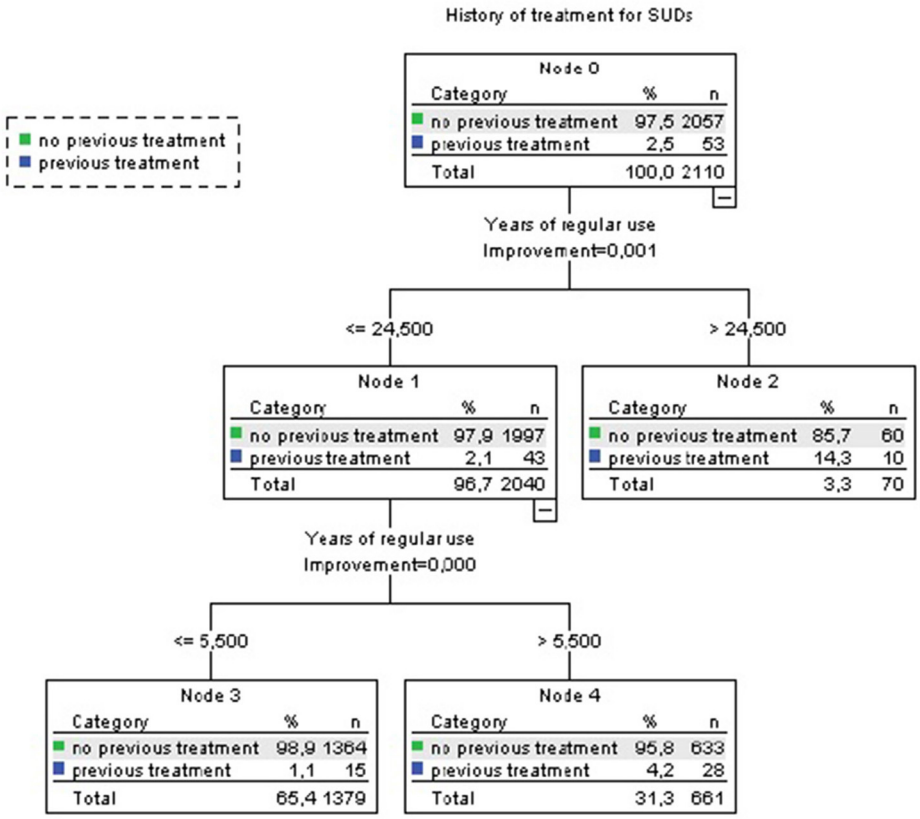

FIGURE 6 | CART analysis (Treatment for SUDs). Accuracy 97.5%. Independent variables included: mg THC per day of use last month, years of regular use.

SDS score correlated with mg THC per day of use last month (0.365, $p < 0.001$) and days of use last month (0.474, $p < 0.001$). CART analyses identified a subgroup of higher risk of SDS >4 (which is indicative of a cannabis use disorder) in those who used cannabis at least 28.5 days per month (61.9 vs. 33.6% of whole subsample, see **Figure 7**). PHQ score correlated inversely with years of regular use (−0.148, $p = 0.018$). Previous treatment for SUD was associated with years of regular use (mean 9.7, SD 7.8 no previous treatment vs. mean 15 years, SD 9.3 previous treatment, $p = 0.002$). History of motor vehicle accidents was associated with years of regular use (mean 9.4, SD 7.8 no motor vehicle accidents vs. mean 12.9, SD 8.2 motor vehicle accidents, $p < 0.001$). Cognitive impairment was associated with years of regular use. In this case, longer use was associated with lower probability of cognitive impairment (mean 10.6, SD 8.3 no cognitive impairment vs. mean 8.4, SD 6.8 cognitive impairment; $p = 0.02$). Other outcomes were not associated with any patterns of cannabis use.

DISCUSSION

The relationship between cannabis use and health harms is a complex phenomenon. Among all these potential health harms, cognitive, and behavioral consequences are the best studied and described in the literature. This study analyzes the relationship between acute, early, and chronic exposure and several indicators of cognitive and behavioral harm. The vast majority of previous research did not include several dimensions of pattern of use; specifically, they did not take into account quantity and the combination of early, acute, and chronic exposure. Clarifying the influence of each of these dimensions on cognitive and behavioral harm is a necessary first step to eventually develop instruments that might allow clinicians to straightforwardly identify those users who are more prone to suffer from psychological or behavioral harm related to cannabis and thus providing targeted further assessment and treatment.

Our results suggest that using cannabis 3 out of 4 days increases eight times the probability of scoring 4+ on the SDS, which is indicative of a cannabis use disorder. Also, in our sample, a start of regular cannabis use before 25 years old combined with using cannabis at least once per month is associated with higher probability of risky alcohol use. Besides, a start of regular cannabis use before 18 years old combined with a period of regular use of at least 7.5 years was associated with 80% higher odds of motor vehicle accidents. On the other hand, results were ambiguous regarding the role that age of first use and milligrams of THC per day of use might play regarding cannabis-related harms.

In our sample, we could not find a clear association between acute, chronic, or early cannabis exposure and

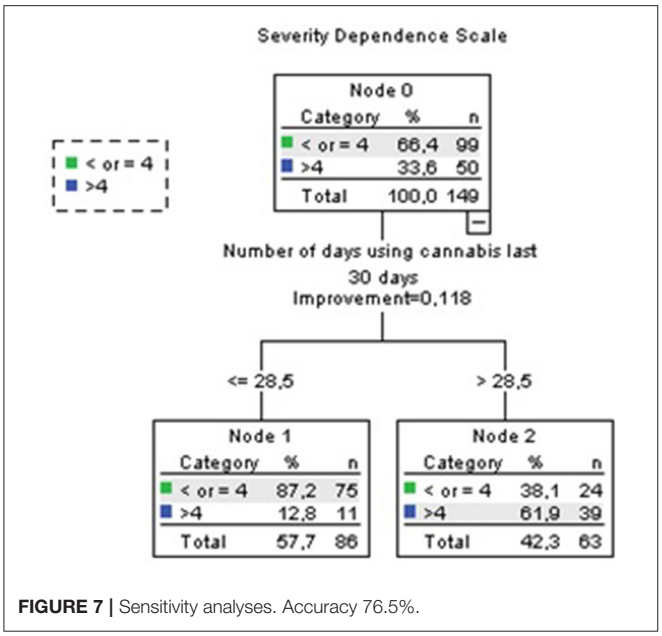

FIGURE 7 | Sensitivity analyses. Accuracy 76.5%.

violence, gambling, sleep disorders, cognitive impairment, suicidal impulses, anxiety, and depression. Several arguments rise to potentially explain these results. First, violence and suicidal impulses were evaluated through *ad hoc* questions because otherwise the questionnaire would have been too long. Unvalidated questions may not detect existing harms in these dimensions. Second, the cannabis use indicators included in this study might not be sufficient to explain these harms. Other variables [e.g., number of heavy cannabis use days and high-potency cannabis (8)] might explain better those harm indicators. Third, literature shows a different level of evidence between cannabis use and harms. While the relationship between motor vehicle accidents or CUD and cannabis use is well-established, the relationship between gambling, violence, and sleep disorders is less clear (7). Moreover, the mean age of the sample is relatively low (26.2 years old), while some harms (such as suffering a motor vehicle accident or receiving treatment for substance use) might need longer chronic cannabis exposure (35, 36).

Our findings that frequency of use is associated with severity of dependence are consistent with previous research. For instance, a recent systematic review concluded that the most consistent predictive factors of cannabis dependence were an early onset of cannabis use, frequent use, and prior drug involvement. Comorbid mental disorders like affective disorders, anxiety disorders, and alcohol-related disorders also seem to predict first incidence of cannabis dependence (18). Our results suggest that frequency of cannabis use of 3 out of every 4 days (or more than 21 days per month) increased severity of cannabis dependence (SDS >4). This would be a higher threshold than the ones proposed in most previous literature. For instance, a recent cross-sectional study pointed to a threshold of cannabis use at least two to three times a month for increased probability of suffering a cannabis use disorder or psychosocial functioning cannabis-related problems when quantity of use was at least one joint (37). Also, a cohort study of Australian secondary students suggested a threshold of weekly cannabis use during adolescence for increased probability of cannabis use disorders (38). Nonetheless, other previous studies had already pointed to near-daily or daily frequency of cannabis use for increased risk of cannabis use disorders (39, 40). According to previous studies, younger age at first cannabis use seems to be of crucial importance to the development of dependence. Previous studies stated that an early onset of cannabis use and persistent cannabis use were markers of increased risk of cannabis dependence. Adolescents with daily and weekly use in adolescence (aged 14–17) were more prone to develop dependence later at 24 years of age (41).

Our findings also suggest that a start of regular cannabis use before the age of 25 combined with using cannabis at least once per month might predict higher probability of risky alcohol use. The relationship between alcohol use and increased risk of cannabis-related health harms has been extensively described in previous literature. For instance, in one study, cannabis use appeared to be a marker of cannabis dependence symptoms only in participants who consumed alcohol frequently or in large amounts (42). In another study, lifetime diagnosis of alcohol dependence has been found to increase the risk for lifetime cannabis dependence (43). On the other hand, although alcohol and marijuana/cannabis are frequently used simultaneously, studies suggest that acute negative consequences of co-use are associated with using more than one alcohol product (44).

Particularly, the fact that our results suggest that an early onset of regular cannabis use and frequent use are associated with increased probability of risky alcohol use are in line with a recent latent trajectory analysis study of a longitudinal birth cohort that suggested that individuals with early onset of cannabis use and at least weekly use by age 20 had increased odds of suffering from alcohol dependence (45). Conversely, another cross-sectional study proposed that individuals that consumed cannabis more than once per week in the last 30 days had a higher probability of risky alcohol use (46).

Our data tentatively imply that cannabis users who experience mental health problems might tend to initiate regular cannabis use at earlier ages, which is consistent with previous studies on the relationship between early cannabis exposure and psychiatric disorders, especially psychosis (20).

Also, in our sample, although the respondents who had used cannabis for 24.5 years had received treatment for SUDs more frequently than those who only used cannabis for periods of <6 years, after adjusting for age, gender, use of other illegal drugs, and tobacco use, years of regular use was not associated with treatment for SUDs. However, several previous studies imply that cannabis use is associated with use of other substances, both concurrent (46) and in later stages of life (47). Also, previous literature described a doubling in the number of individuals entering specialized drug treatment for cannabis-related problems for the first time in EU between 2003 and 2014 (48). Similar increases have been less consistent for other illicit drugs, and cannabis problems appear to be responsible for an increasing percentage of all new drug treatment demands (49). Considering all that, it would be coherent to assume that individuals that consume higher THC doses or that have been

consuming cannabis for longer periods of time are more prone to be treated for any SUD.

Sensitivity analyses of those who reported regular use since before 18 years old ($n = 517$) showed a high risk of SDS >4 (which is indicative of a cannabis use disorder) among those who smoked daily or almost daily (62% of them). As in the whole sample, interpretation of the association between patterns of use with cognitive impairment and PHQ score is challenging. In this subsample, motor vehicle accidents and previous treatment were only associated with years of regular use, with little impact of quantity or frequency. This might translate into years of regular use having a specific weight in the impact on motor vehicle accidents and previous treatment among those who started to use cannabis regularly earlier being quantity and/or frequency more relevant for those who started later.

Lastly, we should note that according to our data, a start of regular cannabis use before 18 years old combined with a period of regular use of at least 7.5 years is associated with higher probability of motor vehicle accidents. A systematic review published in 2010 linked fatal motor vehicle accidents mostly with frequency and quantity of use criteria, specifically more than 50 occasions of use by age 18 or smoking more than 10 joints per week (25). More so, the association between cannabis use and motor vehicle accidents has been described extensively in the literature (7). Previous studies reported that marijuana use by drivers is associated with a significantly increased crash risk. The crash risk appears to increase progressively with the dose and frequency of marijuana use (50). Most past studies highlighted the relationship between acute cannabis use and the collision. For instance, in a sample of 860 injured drivers presenting to Canadian emergency departments due to a traffic collision, controlling for other substance use and acute cannabis consumption, measured through blood sample or self-report, was associated with a 4-fold increase in the risk of a traffic collision, and the association remained when employing a usual frequency control condition (51). Interestingly, our results suggest that not only acute cannabis exposure but also early and chronic exposure could point to higher risk for crash accidents.

LIMITATIONS AND STRENGTHS

Several limitations of our study are pointed out. On the one hand, this is a cross-sectional study, with well-known limitations to assess causality between patterns of cannabis use and health-related harms. Also, although collection of data with a self-administered questionnaire accessible through an online survey allows the recruitment of a big sample size, the sample may be biased by self-selection, i.e., persons with problem of cannabis use may be differentially prone to participate, requiring further validation of results (52). Our results were obtained only from people living in Spain (Europe), which might hamper generalization of the results to other sociocultural contexts. In addition, the pattern of cannabis use and also other substance use could only be assessed by self-reported measures. Nonetheless, literature shows that self-reported substance use, including cannabis, correlates in a fairly precise manner to positive urine toxicology tests (53). In fact, some authors have stressed that history and scales are more reliable than drug screening for cannabis use detection (54, 55). Furthermore, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) recognize self-reporting as a tool for drug approval during clinical trials. Besides, to our knowledge, this is the first survey that assessed cannabis use and health-related harms that applied a cannabis dose standardized measure [the Standard Joint Unit (27)] to convert individual self-reports of cannabis use (joints and grams used the last month and money spent on cannabis during the last month) to milligrams of cannabis main psychoactive constituent (THC).

Also, experiencing some of the behavioral harms assessed (such as motor vehicle accidents or receiving treatment for substance use) is highly age-dependent, so results regarding the relationship of these harms with dimensions of pattern of use that are also age-dependent, such as years of chronic use, should be interpreted with caution.

To summarize, the cross-sectional design of our study does not allow us to establish causality or to assuredly define the threshold for frequency, quantity, age of first use, age of initiation of regular use, or years of regular use that affect harm, but our results increase the evidence in favor of considering not just frequency of use but also other dimensions of cannabis use in both research and clinical practice.

The relationship between pattern of cannabis use and neuropsychological harm is a complex phenomenon, even more so when considering that cannabis psychoactive constituents disrupt the natural functioning of the endocannabinoid system, that affects both central nervous system (CNS) and peripheral processes and plays a role on anxiety, depression, neurogenesis, reward, cognition, learning, and memory (56, 57). Further, research efforts with longitudinal data should be made in order to have a better understanding of how all these five dimensions interact together to determine neuropsychological harms.

CONCLUSIONS

Using cannabis 3 out of 4 days might increase up to eight times the probability of scoring 4+ on the Severity Dependence Scale, which is indicative of a cannabis use disorder. Also, a start of regular cannabis use before 25 years old combined with using cannabis at least once per month might increase probability of risky alcohol use. Besides, a start of regular cannabis use before 18 years old combined with a period of regular use of at least 7.5 years was associated with increased risk probability of motor vehicle accidents. The pattern of cannabis use should be carefully and widely evaluated—not just the frequency of use but also other dimensions—in research to assess cannabis-related harms. In order to have a better understanding of what kind of cannabis use predicts higher risk for experiencing cognitive and behavioral harms, future research with longitudinal data needs to determine the single independent contribution of each cannabis use indicator to experience harm. This could allow determining cutoffs for the relevant indicators, since it offers healthcare providers a practical tool to identify consumers at

risk. This would also facilitate early preventive strategies and better monitoring of treatment interventions aimed at risk and harm reduction.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because database is under analysis for other studies. Requests to access the datasets should be directed to Eugénia Campeny, campeny@clinic.cat.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Hospital Clínic de Barcelona (HCB/2017/0795) according to the Helsinki Declaration (update Fortaleza 2013) and the national regulations.

AUTHOR CONTRIBUTIONS

MB-O, AG, EC, and HL-P designed the study. EC, HL-P, CO, and MB-O wrote the first draft of the manuscript. All the other authors reviewed and approved the final paper.

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SUPPLEMENTARY MATERIAL

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REVIEW
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Cannabis, Impaired Driving, and Road Safety: An Overview of Key Questions and Issues

Bruna Brands[1,2,3]*, *Patricia Di Ciano*[2,3,4]* and *Robert E. Mann*[2,4,5]

[1] Health Canada, Ottawa, ON, Canada, [2] Institute for Mental Health Policy Research, Centre for Addiction and Mental Health, Toronto, ON, Canada, [3] Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada, [4] Campbell Family Mental Health Research Institute, Toronto, ON, Canada, [5] Dalla Lana School of Public Health, Toronto, ON, Canada

The road safety impact of cannabis has been a topic of much discussion and debate over the years. These discussions have been revitalized in recent years by initiatives in several jurisdictions to legalize non-medical cannabis. Canada became the second country to legalize non-medical cannabis use in October, 2018, preceded by Uruguay in December 2013. Road safety concerns were key issues in the Canadian government's deliberations on the issue. In this paper, we identify several key questions related to the impact of cannabis on road safety, and provide a consideration of the relevant literature on these questions. These questions cover several perspectives. From an epidemiological perspective, perhaps the central question is whether cannabis use contributes to the chances of being involved in a collision. The answer to this question has evolved in recent years as the ability to conduct the relevant studies has evolved. A related question is the extent to which cannabis plays an important role in road safety, and recent research has made progress in estimating the collisions, injuries, and deaths that may be attributed to cannabis use. Several questions relate to the behavioral and pharmacological effects of cannabis. One central question is whether cannabis affects driving skills in ways that can increase the chances of being involved in a collision. Another important question is whether the effects of the drug on the driving behavior of medical users is similar to, or different from, the effects on non-medical users and whether there are sex differences in the pharmacological and behavioral effects of cannabis. Other important questions are the impact of tolerance to the effects of cannabis on road safety as well as different routes of administration (e.g., edibles, vaped). It remains unclear if there is a dose-response relationship of cannabis to changes in driving. These and other key questions and issues are identified and discussed in this paper.

Keywords: cannabis, driving, impaired-driving, medical, non-medical

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The University of Manchester, United Kingdom

***Correspondence:**
Bruna Brands
bruna.brands@canada.ca
Patricia Di Ciano
patricia.diciano@camh.ca

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INTRODUCTION

Cannabis came under national and international regulation in the twentieth century [e.g., (1)], and for most of that century medical and non-medical use of the drug was illegal in most developed countries. However, in the latter half of the twentieth century, many began to question the wisdom of prohibiting cannabis use [e.g., (2)] at the same time as research began to appear suggesting that cannabis may have legitimate medical uses (3). As well, others examining the harms created by

cannabis in comparison to other drugs observed that cannabis did not appear to be as harmful as the legal drugs tobacco and alcohol, further questioning the legitimacy of prohibition (4). Thus, toward the end of the twentieth century several jurisdictions had authorized cannabis use for medical purposes, and in the early years of the twenty-first century several jurisdictions have legalized cannabis for non-medical use (5). However, one area where evidence provides strongest support of an adverse impact of cannabis is its impact on traffic safety (6), and thus, the movement to legalization has brought increasing interest in the road safety impact of cannabis and how any negative effects might be addressed.

Understanding and addressing road safety problems resulting from cannabis is a complex challenge that requires insights from a variety of research fields, including pharmacology, epidemiology, and behavioral sciences, among others. While impaired driving is an international issue that affects every country (7), our understanding of driving under the influence of cannabis (DUIC) has largely been derived from studies conducted in higher income countries. However, important recent studies are confirming that DUIC is a road safety issue in lower income countries as well (8, 9). Studies have also focused on the impact of cannabis on drivers of automobiles. Nevertheless, it is clear that other road users, such as pedestrians and cyclists, may be under the influence of cannabis (9, 10), and the first study to assess the impact of cannabis on the injury risk of cyclists provided some evidence that cannabis may increase their risks of injuries resulting from crashes (11).

The increased attention to the road safety impact of cannabis in recent years has expanded our understanding of this topic, nevertheless many questions remain. In this paper we provide an overview of key questions related to cannabis and road safety, and point to current information on each topic as well as significant issues that remain to be addressed. We begin with a consideration of questions arising from epidemiological studies of DUIC. We then consider questions arising from the pharmacology of cannabis and its effects on behavior, including driving behavior.

Does Cannabis Increase Collision Risk?

Perhaps the central question that must first be addressed is whether or not drivers who have recently used cannabis are at increased likelihood of being involved in a collision. Nevertheless, it is only relatively recently that a consensus on this question has emerged. Early evidence on this topic was not conclusive, and in a 1999 review Bates and Blakely concluded that, "There is no evidence that consumption of cannabis alone increases the risk of culpability for traffic crash fatalities or injuries for which hospitalization occurs, and may reduce those risks [(12), (p. 231)]." However, their conclusions were based on a relatively small number of studies addressing questions that were methodologically challenging. Since then, much more research on this topic has appeared, employing more rigorous methodologies, and current information suggests a different conclusion. Three meta-analyses have been published that conclude that the acute use of cannabis does increase collision risk (13–15), although the extent of the increase differed across studies. Even so, studies continue to appear suggesting that more needs to be understood in terms of how cannabis might increase collision risk (16). As well, research has yet to establish the characteristics of cannabis-involved collisions, or the impact of cannabis on injury severity resulting from collisions (17, 18).

Who Drives Under the Influence of Cannabis?

If cannabis increases collision risk, it is important for prevention purposes to understand the people who report DUIC. Some factors have been identified that appear to predict an increased likelihood of DUIC. These include being an adolescent or young adult (19–21), experiencing cannabis-related problems (22), and possibly being a medical cannabis user [as opposed to a recreational cannabis user (23)]. As well, risk taking propensities, including reporting driving after drinking, also appear to be associated with increased likelihood of DUIC (21, 22). However, it should be noted that most research on the characteristics of people who report DUIC is derived from studies conducted where or when use was illegal, and thus it is possible that these characteristics may differ in legalized cannabis environments (24).

Does Cannabis Play an Important Role in the Road Safety "Big Picture"?

For many years, the impact of cannabis on road safety received relatively little attention, in part because attention of researchers was focused on other topics such as alcohol and traffic safety. However, as noted the topic of cannabis and road safety has received much more attention, to the point where some initial estimations of the role of cannabis in the larger road safety picture could be estimated, as has been done with alcohol (25). Wettlaufer et al. (26) were able to estimate the total numbers of fatalities, injuries, and collisions, as well as the estimated social costs, that could be attributed to driving under the influence of cannabis in Canada in 2012, based on estimates of the impact of cannabis on the odds of collision involvement [e.g., (13)] and the prevalence of DUIC, among other things (26). They estimated that in Canada in 2012, cannabis attributable collisions accounted for 75 deaths and 4,407 injuries, with an additional 7,794 individuals involved in property-damage only collisions, which resulted in estimated costs of over $1 billion (CDN), using willingness to pay methods. The largest portion of casualties and costs resulted from collisions involving young drivers, since they are most likely to drive under the influence of cannabis.

How Does Cannabis Affect Driving Behavior in Ways That Influence Collision Risk?

In order to fully understand the road safety impact of cannabis, and identify appropriate responses to that impact, it is important to understand how cannabis affects driving behavior. A small number of studies have employed observational studies of drivers given cannabis to consume (27), but these studies present important challenges to implement and carry out safely. One safe and objective means of studying the effects of psychoactive drugs on driving in the laboratory is with a driving simulator. Simulator

research provides a controlled means of studying a variety of variables that cannot be easily controlled in the real world. For example, comparisons of driving in different situations (day vs. night, rural vs. urban) are challenging in on-the-road situations. Perhaps most important for the study of psychoactive drugs, the safety of the simulator cannot be understated, and studies of the effects of psychoactive substances with known impairing effects are likely best conducted in a safe, controlled, environment.

LABORATORY STUDIES

Laboratory studies of the effects of cannabis on driving date back many decades. The findings of these early studies need to be considered within the context of the changing landscape of non-medical cannabis use. Over time, it is known that the potency of recreational cannabis has steadily increased, and cannabis now has upwards of 10% THC, with some potency estimates as high as 19–22% (28–30). Thus, the utility of some of the early research using low potencies of THC (e.g., 1–3%) is limited in our modern world. For this reason, we will focus this review on studies published on or after the year 2000. Throughout, potencies of cannabis are provided for the cited studies.

The present overview of laboratory studies of the effects of cannabis on simulated driving will be structured into several themes. The first section will focus on findings using different routes of administration of cannabis. Next, claims of tolerance to the impairing effects of cannabis in frequent users will be evaluated. Differences in the effects of cannabis on driving in males and females will be explored, as will dose-response relationships of cannabis to driving and THC. Finally, the effects of medical cannabis on driving will be reviewed.

Different Routes of Administration

Smoking

Smoking remains the most common route of administration (31), and thus, it has appropriately been the route of administration most frequently studied in simulator studies. It is estimated that about 84% of people who report past year use of cannabis have smoked their cannabis (31). Simulator studies have generally used between 1.77% THC and 6.7% THC in the studies, or 10–30 mg of THC in a cigarette. These represent low doses.

With respect to the use of cannabis, simulator studies have found important changes in driving after use of smoked cannabis. Consistent with epidemiological data (32, 33), one study found an increase in collisions after use of cannabis (34). Perhaps the most consistent finding with smoked cannabis is an increase in Standard Deviation of Lateral (SDLP), a measure of weaving (35–37). Despite increases in SDLP no effects on inappropriate lane crossings (37, 38) or lane position (34) were found [but see: (39)]. Similarly, steering angle was not affected (36), while steering control was decreased at a low dose in one study (39) but not another (34). Another finding that has been reported is changes in measures of speed. In general, cannabis decreases speed (36, 39–41) and speed variability (39). Measures of reaction time are also increased (36, 39). However, no effects on brake latency were found in other studies (42, 43). Increased headway (36) was also reported. Finally, one study reported an increase in "penalty points" after 900 micrograms/kg of THC in cigarettes. Penalty points were assigned for various driving infractions (44).

Vaporized

Vaping has recently received a great deal of media attention, due to concerns over the safety of this route of administration. In the real world, about 27% of cannabis users vape using a pen or e-cigarette, while 15% use a vaporizer (31). At the time of writing, only a few studies examined the effects of vaped THC on simulated driving. In one study, participants vaped 11% THC. Consistent with the smoked route, vaped THC increased SDLP (45), when required to follow and maintain a given distance to the car ahead (46). In this same task, no effect on headway was found. When instructed to follow GPS segments on highway and rural roads, no effects of THC were found. In another study, participants vaped 12.9% THC and the only effect observed was on crash risk at 1, 3, and 5 h post-cannabis (47). No effects were seen on braking reaction times, steering reaction time, lane-keeping speed control, intersection crossing, vigilance, obstacle avoidance accuracy, and obstacle avoidance crash risk. Thus, the effects of vaped THC seem to vary depending on the task parameters, but clearly more research is required.

Oral

Approximately 46% of people who use cannabis consume their cannabis in food (31). Thus, it is of interest to determine the effects of cannabis edibles on driving. At present, we are not aware of any published studies of the effects of cannabis edibles on simulated driving. However, clues as to the impact of the oral route of administration on driving can be obtained from the effects of synthetic THC, in the form of dronabinol. In one study with a crossover design with two doses of oral dronabinol (10 and 20 mg) or placebo, participants drove at a constant speed on a rural road or behind a lead car in a car-following task. Dronabinol increased SDLP, but did not affect speed measures (48). In another study with oral dronabinol (0, 10, and 20 mg), SDLP was also increased, as was reaction time (49). There were no effects on gain or coherence. In this study, gain was defined as the degree of reaction to speed changes to the car in front, while coherence was the degree to which the patterns of speed changes for lead and following car corresponded.

Frequent vs. Occasional Users

The repeated use of cannabis can, under certain conditions, lead to tolerance to some of its effects (50, 51). However, recent meta-analyses of the effects of repeated cannabis in humans have yielded equivocal conclusions. For example, one meta-analysis concluded that there is tolerance to some cognitive measures, such as changes in EEG and to the intoxicating effects of THC (50). Findings from studies of psychomotor function, attention and memory were mixed (51).

Findings of tolerance to the effects of cannabis on driving are also mixed. At present, there have been very few studies of the effects of frequent cannabis use on simulated driving. In one study, driving impairments following a low dose (1.8–3% THC) of smoked cannabis were worse in regular cannabis users

compared to non-regular users (52), suggesting that there was no tolerance of the effects of cannabis on driving. In another study, weaving was more evident in occasional users, as compared to regular users after oral synthetic THC (dronabinol) (48), suggesting that regular users may become tolerant to the effects of cannabis. SDLP was also greater in occasional users in another study that administered 10 or 30 mg of THC in a smoked cigarette (35). Further studies are warranted to investigate the effects of repeated cannabis use on driving following smoked recreational doses of cannabis.

It is of note that some recent studies found that heavy, chronic users of cannabis were impaired on the driving simulator, even in the absence of acute intoxication. In one study (53), compared to healthy controls, chronic cannabis users hit more pedestrians, missed more stop signs, made fewer stops at red lights, drove faster, and made more centerline crossings. In another study, chronic cannabis users had slower reaction times, deviated less in their speed and drove slower than the car ahead (54). They did not differ in lane position, speed, car following, off-road accidents, collisions and pedestrians hit. Clearly, tolerance to the effects of cannabis on driving has road safety implications and more research is needed.

Effects of Sex

Sex appears to have important relationships with cannabis dependence. For example, more men than women use cannabis (55), although this gap is narrowing. Despite this, women show a greater progression to dependence than men (56), which may be related to the more severe withdrawal from cannabis that is reported by women (57). In our preliminary study with recreational users, we investigated sex differences in physiological and subjective effects (58). We found that females and males reported similar subjective and cognitive effects of cannabis, despite the observation that males had almost twice the blood level of THC as compared to females, and that males smoked more of the cannabis cigarette than females.

In one study which directly compared the effects of cannabis on driving in males to females (40), it was found, consistent with our findings, that more men than women finished the entire cigarette with 2.9% THC. Despite this, women rated themselves as feeling higher than males, and males were less sleepy than females. Thus, it appears that females were more sensitive to the subjective effects of cannabis than males. Despite this, there were no differences in measures of driving. A related paper by the same group also found no sex differences in cognitive effects of cannabis, despite the fact that males smoked more than females (59).

THC AND DRIVING

As discussed above, there is good consensus that cannabis increases the risk of collision and alters SDLP and sometimes speed in simulator studies. Given the risks of using cannabis prior to driving, some jurisdictions have adopted limits on blood levels of delta-9-tetrahydrocannabinol (THC) while driving. These limits are generally in the range of 2–5 ng/ml. Given the success of limits on breath alcohol levels, it would be of interest to determine cut-off levels of THC for driving. A recently published paper by Arkell et al. (60) concluded that there is a poor and inconsistent relationship between levels of THC in biological fluids and degree of impairment. This led them to conclude that *per se* limits cannot discriminate between impaired and unimpaired drivers. They also concluded that more research is needed. It should be noted that he study that they used to test their hypothesis involved occasional users.

From the studies published thus far, it appears that there is a dose-response relationship of THC to changes in driving. For example, in one study, it has been reported that SDLP was increased by THC (46). Another study found that increasing blood THC was associated with decreased mean speed and increased following distance, with effects being observed at THC levels as low as 2 ng/ml (61). Changes in speed and reaction time were also dose-dependent (36, 39, 52), but THC was not measured in these studies. In another study, impairments, measured as "penalty points" were seen at 15 ng/ml of THC in blood (44). Nevertheless, more research is needed to gain a better understanding of the relationship between blood levels of THC and alterations in driving behavior (60).

We have recently published a paper that explored the relationship of THC to driving (41). In this study, participants drove a simulator at 30 min, 24 and 48 h after smoking a cannabis cigarette with 12.5% THC or placebo, in a parallel groups design. THC in blood was analyzed throughout the session, and participants were divided into high THC groups and low THC groups based on a median split of THC in the blood. We found that the high THC group drove significantly slower 30 min after smoking, as compared to placebo. Under dual task conditions, both the low THC and high THC groups drove slower. With respect to SDLP, the high THC group was different from placebo at 30 min and 48 h after smoking cannabis under single task conditions. There was no effect of cannabis on SDLP under dual task conditions. Thus, important evidence for a dose-response relationship was found, indicating that THC levels in blood may be related to changes in driving.

THC and Driving After the Medical Use of Cannabis

Many jurisdictions have adopted *per se* laws in an attempt to curb DUIC, regardless of whether cannabis is used recreationally or for medical reasons. Despite these types of laws, courts in some jurisdictions of the world have seen challenges, in which medical users assert that their driving is unaffected by cannabis use due to the development of a drug tolerance associated with more frequent use. However, to date, there has been little research attention specifically on the effects of medical cannabis use on driving. This gap in the literature is dangerous given the prevalence of medical use of cannabis: 13% of cannabis users in a recent Canadian survey indicated that they used cannabis for medical purposes (31), and only half of these had a medical authorization (62). It is estimated that over half of those who use cannabis for medical purposes have driven within 2 h of using cannabis (63, 64) and most of these users indicated that there was "no risk" or "slight risk" of driving after the medical use

of cannabis (64). Indeed, *many believe that therapeutic cannabis users are able to drive safely after using the drug* (65).

In another of our studies, we investigated the effects of cannabis on simulated driving in participants who use cannabis for medical reasons (64). In this study, we found that, consistent with our findings from recreational users, mean speed was decreased. Decreases in speed were similar to those observed in the recreational users, suggesting that medical users do not become tolerant to the effects of cannabis on driving. Thus, our findings suggest that "cannabis is cannabis" and it produces impairments in driving, regardless of whether it used for recreational or medical purposes. In our published study, we also observed that blood levels of THC were increased after smoking cannabis for medical reasons. The levels of THC in the blood did not show any evidence of tolerance when compared to THC levels after smoking cannabis for recreational purposes. Thus, medical users of cannabis should exercise caution in driving after the use of cannabis for medical purposes.

What Levels of Cannabis in the Body Are Consistently Associated With Impairment?

There are a number of sources of information relevant to the question of what levels of cannabis in the body are associated with impairment. As well the answer to this question is important for considerations of whether or not to introduce a *per se* level, or legal limit, for cannabis and at what level. Laboratory studies of the effects of cannabis on basic behavioral and cognitive tasks, such as simple and choice reaction time, tracking ability, and memory, show that performance on a variety of measures is affected by smoking cannabis or consuming it in other ways (66–68). Nevertheless, the level at which impairment can be reliably seen has been a more controversial topic. Some have suggested that the effects of cannabis are not sufficiently dose-related to permit the identification of these levels. While the number of studies showing impairing effects of cannabis on driving-related skills is increasing, it is true that far fewer studies address the issue of whether that impairment is related to dose or level of THC in the body. Nevertheless, in laboratory studies of cognitive and behavioral effects there is evidence that the effects of cannabis increase as the dose consumed or level of THC in blood increases (69, 70). Evidence that effects of cannabis on driving simulator performance and collision risk increase as dose consumed and levels in the body increase has also been reported (71).

Based on these observations, *per se* levels for cannabis supported by evidence have been proposed. These levels have been based on literature reviews or meta-analyses of efforts to identify comparable levels of impairment caused by THC and specific levels of alcohol in the body. Grotenhermen et al. (72) proposed that serum levels of cannabis between 7 and 10 ng/ml caused levels of impairment that were comparable to Blood Alcohol Levels (BALs) of 0.05%. Vindenes et al. (73) suggested that 3 ng/ml of THC in whole blood was comparable to a BAL of 0.05%, and that 9 ng/ml of THC in whole blood was comparable to a BAL of 0.12% BAC (73). In the comprehensive European DRUID project, investigators concluded that 3.8 ng/ml of THC in serum was equivalent to a BAL of 0.05% (74).

CANNABIDIOL AND DRIVING

Cannabis contains a number of ingredients, and apart from THC, cannabidiol (CBD) has received the most widespread research interest. The proportion of THC to CBD may vary in cannabis, and thus it may be possible to develop strains of cannabis that reduce the risk of THC to driving. Within this context, a recent review of the effects of THC:CBD oromucosal sprays on driving did not find an impairment in driving in patients with multiple sclerosis who were using CBD:THC oromucosal sprays to treat their symptoms (75). Specifically, 80–90% of respondents reported no change in driving ability as a result of use of the THC:CBD oromucosal spray. This suggests that CBD may not impact driving ability. Although compelling, the studies here were observational in nature and focused on THC:CBD combinations; no experimental studies of the effects of CBD alone on driving have been conducted.

A recent study examined the possibility that CBD may impact the effects of THC on driving. In this study with a crossover design (45), participants vaped 11% THC, THC/CBD (11% THC, 11% CBD) or placebo. The THC/CBD condition increased SDLP to the same extent as THC alone, suggesting that CBD does not affect THC-induced changes in driving. Further, there were no effects of any of the conditions on headway, but the CBD/THC condition had greater standard deviation of headway than placebo. Thus, there is some evidence that combinations of THC and CBD may negatively impact driving. It should be noted that this study used the vaped route, and CBD is often taken orally, thus more studies are warranted, especially given the findings from observational studies and investigation of CBD and THC combinations on cognition. A subsequent study investigate the effects of different strains of cannabis with different proportions of THC and CBD on driving (76). They found that SDLP was increased after THC-dominant strains of cannabis, or after cannabis with equal amounts of THC and CBD, but not after CBD-dominant strains. This suggests that CBD does not impact driving and also does not reverse the deficit in driving observed after cannabis.

HOW LONG DO THE EFFECTS OF CANNABIS ON DRIVING BEHAVIOR LAST?

One concern about the effects of cannabis on driving behavior has been the length of time that impairment might last. This issue has often been confused with the length of time that THC or its metabolites can be measured in blood or other bodily fluids. Trace amounts of THC or its metabolites may be detected for days or even weeks following cessation of use (77). However, simple presence of THC or its metabolites does not mean that driving performance measures are impaired. Instead, similar to the above discussion of the levels of THC at which impairment is observed, the practical question is how long does impairment last following consumption of cannabis.

Some early studies suggested that residual effects of a dose of cannabis might last for 24 h following use (78). Significant impairment of performance on a flight simulator was reported

in two studies (79, 80). Research with driving simulators, however, has not found evidence for impairment extending beyond the first few hours following consumption [e.g., (39, 41)], consistent with measures of subjective effects of the drug. Other investigators have concluded that impairment is linked to blood THC levels, and is highest in the initial period after cannabis use and declines in the few hours after consumption when blood THC levels typically drop below 3–5 ng/ml (81, 82). The development of Lower Risk Guidelines for Cannabis Use at the Centre for Addiction and Mental Health in Toronto, Canada, based on these observations, recommended that an individual who has smoked one cannabis cigarette wait at least 6 h before driving, or longer if feelings of intoxication remain (83).

CONCLUDING COMMENTS

As more jurisdictions move toward legalization of cannabis, regulators are likely to be increasingly concerned with the road safety impact of these changes and how any negative effects can be attenuated or avoided. While in the past there has been controversy over whether cannabis use and DUIC presented road safety risks, more recent research provides converging evidence that DUIC can increase collision risk and may be an important contributor to deaths and injuries resulting from collisions. Young adults appear most likely to engage in DUIC. Acute effects of cannabis on driving-related behaviors may include an increase in weaving, and a reduction in speed. Effects on reaction time have also been reported. This seems true regardless of the route of administration although more research is needed. At present, all studies of the effects of oral cannabis on driving consisted of synthetic THC (dronabinol) and no studies of cannabis edibles have been published. Evidence also exists to identify levels of cannabis in the blood at which impairment is observed and which thus may be proposed as *per se* levels for legal initiatives to deter DUIC. Nevertheless, important questions remain to be answered. Currently, little is known about the types of collisions most likely to involve cannabis, or if cannabis affects injury severity. More research is needed to understand sex differences in the effects of cannabis. Other questions include the comparative pharmacology of different modes of administration of THC (for example, are the effects of smoked cannabis and edible cannabis the same?) and different doses of THC and the extent to which regular or frequent uses may develop and display tolerance to the impairing effects of cannabis on driving behavior. As well, more investigation of the potential impairing effects of cannabis on therapeutic users is also warranted. Important questions still remain as to the duration of the effects of cannabis on driving and the time course of safe use of cannabis. Time course studies are especially important for different routes of administration that may have different pharmacokinetics.

AUTHOR CONTRIBUTIONS

BB, PDC, and RM: conceptualization, methodology, and writing—review and editing. PDC: writing—original draft preparation. BB: project administration. All authors have read and agreed to the published version of the manuscript.

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Age- and Sex-Related Cortical Gray Matter Volume Differences in Adolescent Cannabis Users: A Systematic Review and Meta-Analysis of Voxel-Based Morphometry Studies

*Aliyah Allick[1,2], Grace Park[1,2], Kwon Kim[1,2], Michelle Vintimilla[1,2], Krutika Rathod[1,2], Rachael Lebo[3,4], Julie Nanavati[3] and Christopher J. Hammond[1,2,5]**

[1] Division of Child and Adolescent Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [2] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [3] Welch Medical Library, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [4] I.D. Weeks Library, Health Sciences Department, University of South Dakota, Vermillion, SD, United States, [5] Behavioral Pharmacology Research Unit, Johns Hopkins University School of Medicine, Baltimore, MD, United States

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***Correspondence:**
Christopher J. Hammond
chammo20@jhmi.edu

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Introduction: Adolescent-onset cannabis use is rising in the era of marijuana legalization. Recent imaging studies have identified neuroanatomical differences between adult cannabis users and controls that are more prominent in early-onset users. Other studies point to sex-dependent effects of cannabis.

Methods: A systematic review following PRISMA guidelines and subsequent effect-size seed-based d mapping (SDM) meta-analyses were conducted to investigate relationships between age (across the 12-to-21-year-old developmental window), sex, and gray matter volume (GMV) differences between cannabis using (CU) and typically developing (TD) youth.

Results: Our search identified 1,326 citations, 24 of which were included in a qualitative analysis. A total of 6 whole-brain voxel-based morphometry (VBM) studies comparing regional GMV between 357 CU [mean (SD) age = 16.68 (1.28); 71% male] and 404 TD [mean (SD) age = 16.77 (1.36); 63% male] youth were included in the SDM-meta-analysis. Meta-analysis of whole-brain VBM studies identified no regions showing significant GMV difference between CU and TD youth. Meta-regressions showed divergent effects of age and sex on cortical GMV differences in CU vs. TD youth. Age effects were seen in the superior temporal gyrus (STG), with older-aged CU youth showing decreased and younger-aged CU youth showing increased STG GMV compared to age-matched TD youth. Parallel findings in the STG were also observed in relation to duration of CU (years) in supplemental meta-regressions. Regarding sex effects, a higher proportion of females in studies was associated with increased GMV in the middle occipital gyrus in CU vs. TD youth.

Conclusions: These findings suggest that GMV differences between CU and TD youth, if present, are subtle, and may vary as a function of age, cumulative cannabis exposure, and sex in young people. Whether age- and sex-related GMV differences are attributable to common predispositional factors, cannabis-induced neuroadaptive changes, or both warrant further investigation.

Keywords: adolescence, cannabis use and dependence, development, age, brain structural alterations, voxel-based morphometry, sex

INTRODUCTION

Cannabis is the most commonly used federally illicit, psychoactive drug by U.S. adolescents and young adults, and the most common drug problem that teens receive substance use treatment for in the U.S. (1, 2). Over 1.6 million adolescents between the ages of 12 and 17 and 7.6 million young adults between the ages of 18 and 25 residing in the U.S. report current use of cannabis (1). In 2018, 24% of U.S. high school seniors reported past-30-day use of cannabis with 6.4% reporting daily use (3, 4). Patterns of cannabis use (CU) have changed among U.S. youth during the era of cannabis legalization. Over the past two decades, legalization of cannabis for medical and recreational use by a majority of U.S. states has dramatically altered societal perceptions of youth and their parents, resulting in a more permissive environment and increased access to cannabis, including new cannabis products (e.g., concentrates, edibles, vaped cannabis) with high concentrations of delta-9-tetrahydrocannabinol (Δ-9-THC), the main psychoactive component of cannabis (5). While population-wide use of cannabis by adolescents has not changed appreciably in the past 10 years, recent studies point to increased prevalence of daily CU and expanded use of concentrates and vaped cannabis among U.S. youth, along with increased prevalence of CU among different subgroups (e.g., college-aged young adults) (5). This is problematic given growing literature that recreational use of cannabis, particularly high-Δ-9-THC-potency cannabis, during adolescence is associated with numerous adverse health outcomes including increased risk for psychiatric disorders, academic failure, and higher rates of morbidity and mortality (6, 7).

The use of cannabis during adolescence may have complex effects on brain structure and function that extend into adulthood (8). While preclinical studies show strong and consistent evidence for a causal relationship between exposure to cannabinoids and changes in brain morphology [see (9) and (10) for reviews], there is conflicting evidence on the long-term effects of cannabis on brain structure in humans (11). Evidence from human structural magnetic resonance imaging (sMRI) studies has been mixed to date, with some studies reporting increased brain volumes related to CU (12) and other studies reporting decreased brain volumes (13) or the absence of volumetric differences between CU and non-users (11). Factors thought to contribute to the variability in human sMRI findings related to cannabis exposure include age of cannabis initiation and onset of regular use, frequency and chronicity of use, co-occurrence/comorbidity of CU with other substance use and substance use disorders such as alcohol and tobacco, and the presence of comorbid psychiatric disorders (11, 14). Many of these confounding factors also emerge during adolescence, a period of increased sensitivity to the negative effects of Δ-9-THC, alcohol, and nicotine exposure (8).

One understudied factor that may account for some of the variance observed in morphologic findings is the age or developmental period at which cannabis exposure effects are investigated. Based upon systematic examination of the adult sMRI literature [see (15) for review], adult studies typically show evidence of decreased gray matter volume (GMV) between CU adults and age-matched non-using controls. Compared to age-matched controls, decreased GMV in CU adults [especially heavy users (15, 16), dependent users (17, 18), and those who initiated cannabis before age 16 (19, 20)] has been observed across diverse brain regions with elevated cannabinoid receptor type 1 (CB1) expression including the medial temporal cortex, temporal pole, hippocampus/parahippocampal gyrus, insula, amygdala, thalamus, prefrontal cortex (PFC), orbitofrontal cortex (OFC), and cerebellum. Relatedly, a recently published meta-analysis of adult sMRI studies showed that regular CU adults had decreased hippocampal and medial and lateral OFC volumes compared to age-matched controls (21). Other adult sMRI studies have shown no neuroanatomical differences between CU adults and age-matched controls (11, 22). Notably absent from this literature are GMV studies in adults that show increased cortical thickness or GMV in relation to cannabis use (21), although one or two studies have reported increased volumes in non-cortical regions including the striatum (23) and cerebellum (15). In contrast, based upon systematic examination of the adolescent sMRI literature [see (24) for review], more variability in morphologic findings is seen, and the opposite pattern of cannabis-related GMV abnormalities is observed, with a number of studies showing larger GMV volumes in CU compared to typically-developing (TD) youth (12, 25, 26). Across these studies, differences in GMV between CU and TD youth are primarily seen in the same brain regions as those observed in CU adults (e.g., amygdala, hippocampus, PFC, cerebellum). Using data from the IMAGEN trial, Orr et al. (12) found evidence for increased GMV in the amygdala, hippocampus, striatum, left PFC, lingual gyrus, posterior cingulate, and cerebellum in a sample of 14-year-old low-level CU compared to age-matched TD youth. Another study by Medina et al. (26) reported increased hippocampal volumes in adolescent CU compared to TD youth. Not all studies have shown increased GMV in adolescent CU compared to

age-matched youth. In addition to studies showing null findings (11), some studies have conversely shown decreased GMV in CU vs. age-matched TD youth (27), although these have been primarily in late adolescent or young adult samples. When taken together, the collective findings across adult and adolescent sMRI studies suggest the possibility of an age/developmental gradient with regard to the effects of cannabis exposure on cortical morphology. As such, age-related influences on the relationship between CU and morphology warrant further investigation, especially across adolescence and young adulthood (ages 12-21 years), the main time period of peak cannabis exposure and cortical maturational changes.

Another factor that could account for variance in morphological findings across studies is the distribution of females-to-male participants in studies. There is growing evidence in support of sex differences in the development, clinical and behavioral presentation, and neural correlates of CU from both clinical and preclinical studies (28). Women begin using cannabis at a later age than men and progress more quickly from first use to dependence (known as the "telescoping" effect) (29), although this pattern is less pronounced in adolescents. Women also report greater abuse-related subjective effects, withdrawal severity, and cannabis-related problems, along with higher rates of comorbid mood and anxiety disorders compared to men (28, 30, 31). In preclinical studies, female rodents show greater sensitivity to the anxiogenic, reinforcing, and sedative effects of cannabinoids (32). While preclinical adolescent cannabis exposure studies largely show widespread desensitization and downregulation of CB1 receptors in the brains of both male and female rodents, some studies also point to sex-specific effects in the cerebellum, hippocampus, PFC, amygdala, and striatum (28, 33). Recent human imaging studies indicate that sex may moderate the relationship between CU and brain morphometry in PFC, ACC, cerebellar, and amygdala regions in adolescents and adults (34, 35). Results from two studies in CU adolescents found that female cannabis users had increased PFC and amygdala volumes compared to female controls, while male cannabis users had smaller volumes or no volumetric differences from male controls (26, 34) [conversely see (36)]. These findings indicate the need for future imaging studies to determine how sex influences the neuroanatomical alterations observed in relation to cannabis exposure in humans.

Given the changing legal status of cannabis and potential for negative downstream effects on health indices for American youth, it is increasingly important to understand the effects of CU on neurodevelopment. Major time sensitive goals of the scientific field today are to determine if neuroanatomical abnormalities emerge as a result of adolescent cannabis exposure, and if present, whether these abnormalities mediate the relationship between cannabis exposure during adolescence and adverse health outcomes in adulthood. Variability in morphological findings across studies in the nascent literature warrant further investigation, especially, to determine whether some of the variance across studies is the result of age/developmental effects or cumulative cannabis exposure, and whether sex-dependent effects are present. Obtaining a comprehensive understanding of neurodevelopmental and sex-dependent effects of CU on GMV requires meta-analysis of sMRI studies examining adolescent boys and girls at various developmental stages. As such, the present study, a whole-brain voxel-based morphometry (VBM) meta-analysis, focused on age-related and sex-related cortical and subcortical GMV differences in relation to CU across adolescence and young adulthood. Using effect-size seed-based d mapping (SDM, also known as signed differential mapping) (37), a coordinate-based meta-analytic approach on whole-brain VBM studies comparing CU and TD youth, our study aims were three-fold: (1) to identify brain regions of increased or decreased GMV in CU relative to TD youth, (2) to explore whether specific regional GMV differences in CU vs. TD youth are age-related (i.e., do they vary as a function of age), and (3) to determine if regional GMV differences in CU vs. TD youth are sex-dependent (i.e., do they vary as a function of the distribution of females-to-male participants in the sample). Based upon previous VBM studies (12, 34), we hypothesized that CU and TD youth would show GMV differences in brain regions with elevated CB1 receptor expression including the medial temporal lobe, hippocampus, amygdala, PFC, OFC, and cerebellum, and that these GMV differences would vary as a function of age and sex. Specifically, we predicted that increasing age across adolescence would be associated with decreasing GMV in these brain regions in CU youth compared to age-matched TD youth and that increasing proportion of female participants in studies would be associated with increasing GMV in these regions in CU youth compared to sex-matched TD youth.

MATERIALS AND METHODS

A systematic review of peer-reviewed studies was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and methods (38). A subset of the studies from the review that included coordinate-level data or parametric maps were used in the SDM meta-analyses.

Search Strategy

We searched for studies indexed in the online databases PubMed/Medline, Cochrane, Embase, and Web Science from January 1990 to November 2019 using the following search terms: "Adolescent"[Mesh] OR "adolescent" OR "young adult" OR "youth" OR "teenager" AND "Neuroimaging"[Mesh] OR "Magnetic Resonance Imaging"[Mesh] OR "MRI" OR "structural MRI" OR "sMRI" OR "voxel-based morphometry" OR "VBM" OR "voxel-based" OR "voxel-wise" OR "neuroimaging" OR "brain circuit" OR "neural" AND "Cannabis-Related Disorders"[Mesh] OR "cannabis use" OR "marijuana use" OR "cannabis abuse" OR "marijuana abuse" OR "cannabis dependenc*[tiab]" OR "marijuana dependenc*[tiab]" OR "cannabis addiction" OR "marijuana addiction" OR "cannabis use disorder" OR "marijuana use disorder" OR "cannabis*[tiab]" OR "marijuana*[tiab]" OR "marihuana*[tiab]" OR "Δ-9-tetrahydrocannabidol" OR "THC". Broad search terms were used to minimize the likelihood of the search not identifying all relevant studies. In addition, we manually scanned the references of included studies and cross-referenced relevant original research, reviews, and meta-analyses to identify studies that may have been missed by the search.

Study Selection

Studies were selected if they met the following criteria: (1) included > 10 participants; (2) participants were between the ages of 12 and 21 years; (3) used diagnostic criteria for cannabis use disorder (CUD) as specified by the DSM (DSM-IV or DSM-5) or described frequency of cannabis use (e.g., daily, weekly, etc.) in study participants; (4) used whole-brain VBM and voxel-wise analyses; (5) reported within- or between-subject contrasts in GMV across cannabis use (CU) and typically developing (TD) control youth, or brain-behavior correlations between GMV and cannabis-related variables; (6) reported coordinates from the above whole-brain analyses in standardized anatomic space [i.e., Talairach or Montreal Neurologic Institute (MNI) space] and (7) provided information about the inclusion/exclusion criteria, clinical characteristics, and demographics of the study sample.

Articles that studied adolescent CU within the context of co-occurring psychiatric disorders were included if studies also included controls that did not use cannabis. Studies with young adult samples were included if they the mean age of participants was below 21 years.

Data Extraction

Articles were extracted, organized, and reviewed using Covidence software (covidence.org). Initial independent title and abstract evaluations were done to identify potential articles of interest by two authors (A.A. and K.R.). Data extraction accuracy showed high correspondence/agreement (>80%) between reviewers. Abstract evaluation was followed by an independent full-text review of articles. Group discussion was used to resolve uncertainties about inclusion criteria and finalize the list of articles included in the qualitative review and SDM meta-analysis.

To facilitate exploration and interpretation of results, studies that examined GMV differences but failed inclusion criteria due to lack of statistical maps or whole-brain analytic approaches were retained for the purposes of qualitative analysis.

To create the final list of studies included in the meta-analysis, we took a three-step approach: Studies identified with the above search that reported coordinates of anatomical differences in CU groups from whole-brain analyses in Talairach or MNI space were identified and marked for inclusion in the SDM meta-analysis. For those studies and for whole-brain VBM studies that provided insufficient information on coordinates, corresponding authors were contacted via email to determine if unthresholded statistical maps or coordinates could be provided. Additionally, we searched NeuroVault (neurovault.org) using select search terms (from above) to try to find unthresholded statistical maps from the relevant studies. These approaches did not yield additional studies or unthresholded statistical maps. Thus, peak coordinates from published data were used for the meta-analysis.

Data Analysis

SDM Meta-Analysis Procedures

All meta-analyses were carried out using the anisotropic effect-size signed differential mapping permuting subject images (SDM-PSI) software, v.6.21 (http://www.sdmproject.com). SDM-meta-analysis is a statistical technique for meta-analyzing neuroimaging data that approach that recreates voxel-level maps of effect sizes and their variance based upon T-maps (37). In contrast to other meta-analytic approaches, SDM enables original statistical parametric maps and peak coordinates to be combined, and reconstructs positive and negative effects within the same statistical maps, preventing a voxel from appearing in opposite directions, and providing for more accurate representation of the results.

Data Coding and Preparation for SDM Meta-Analysis

In preparation for the SDM meta-analysis, the following data coding steps were taken: For studies that met inclusion criteria, coordinates associated with CU groups or variables were manually recorded by two authors (A.A. and C.J.H.). Coded anatomical foci were then double screened for accuracy. If the studies reported coordinates in either Talairach or MNI coordinates, a text file containing the reported coordinates and the t-score associated with those coordinates was created. If a study reported multiple experiments, the results were still reported in the same text file. *P*-values or *z*-values were converted into t-scores using SDM Utilities calculator, otherwise sign of their effect was reported as positive or negative. In addition, a table was made the study identifier (main author), the t-score used to determine significance, and the number of people in the experimental and control groups. If a study reported a statistically significant corrected *p*-value, but didn't give provide sufficient information to transform the corrected *p*-value into a t-score, a t-score of 3.1 was used, providing a conservative estimate. Studies that had no significant peaks were also included. To prepare for the meta-regressions, data on CU and TD youth's age at time of scan, proportion of female participants, age range, average days of cannabis use in past-30-days, and duration of cannabis use (years) were obtained for each study and included as variables.

Meta-Analysis Procedures

The main analysis was conducted in two steps: First SDM meta-analyses were conducted on the statistical parametric maps showing group-level effects for each study to examine for unadjusted differences between youth with CU and matched TD youth. Next, two linear meta-regressions were conducted, one using mean age (years) at time of scan and the other using the proportion of females to males from each study as dependent variables to examine effects of increasing age across adolescence and increasing proportion of female sex on GMV. All models were thresholded using an uncorrected p-value < 0.005 consistent with other SDM meta-analyses (37). Familywise error correction was also carried out using 1,000 permutations, then thresholded using a corrected *p*-value of 0.05.

Reliability Analysis and Supplemental Subgroup Meta-Analyses and Meta-Regressions

To establish the reliability of our meta-analytic results, a jackknife analysis was performed by removing a single dataset and repeating the analysis in sequence. This was done for the primary SDM meta-analysis and meta-regression analyses. Supplemental subgroup meta-analyses were conducted to examine subgroup

effects in (1) studies that controlled for alcohol and tobacco use, (2) studies that excluded youth with comorbid psychiatric disorders, and (3) studies with samples restricted to youth who met CUD diagnostic criteria. Supplemental linear meta-regression analyses were used to examine the influence of (1) age range, (2) mean days of CU in the past 30 days (indexing recent CU), and (3) mean years of cannabis use (indexing duration of CU) on GMV differences between CU and TD youth.

RESULTS

Systematic Review and Qualitative Analysis

The initial search identified 1,327 citations with 822 records excluded following title and abstract screen. Out of 436 citations that underwent full text review, 20 studies examining GMV differences were included in the qualitative analysis, 6 of which met all inclusion criteria. A PRISMA flow diagram

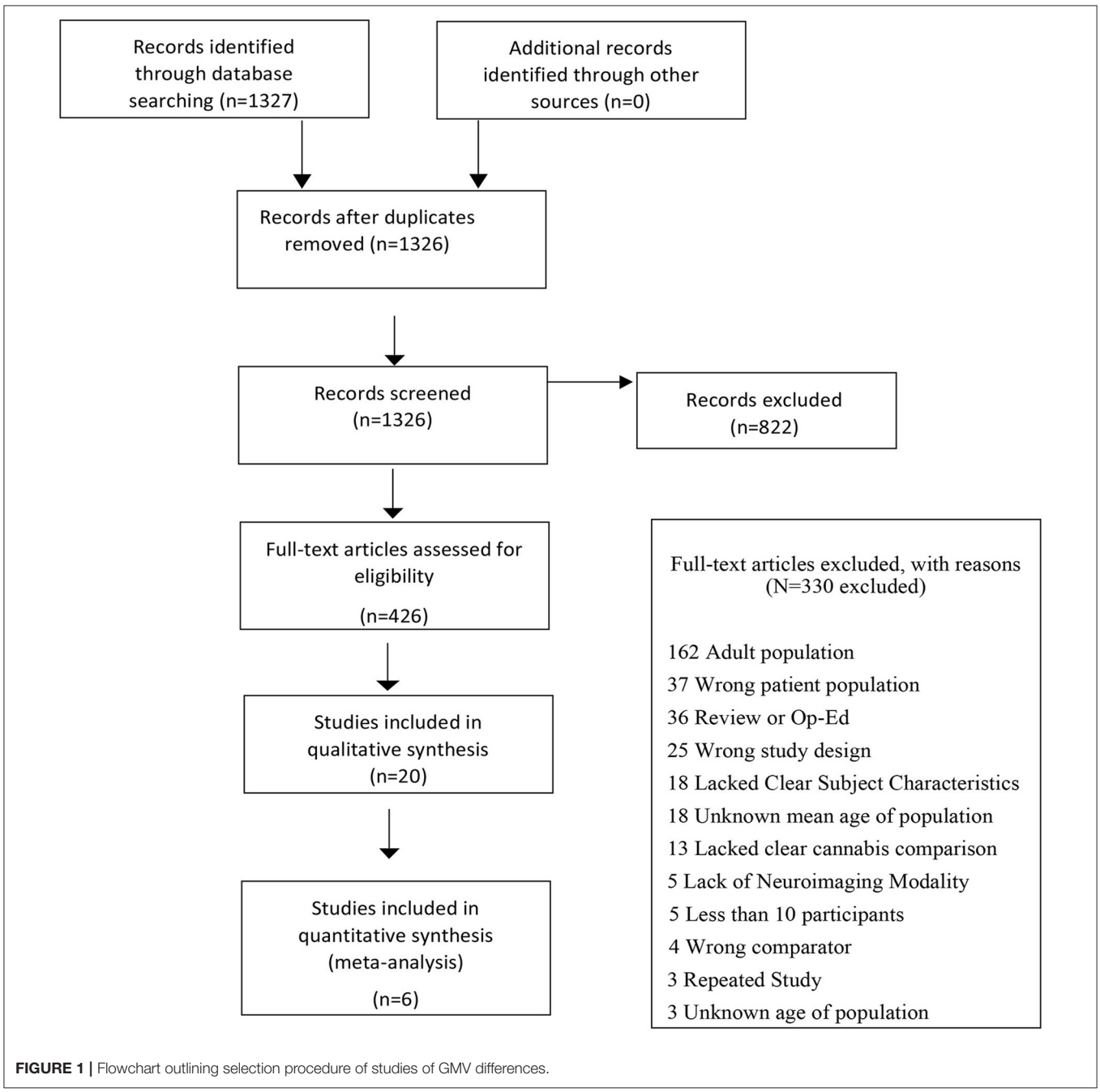

FIGURE 1 | Flowchart outlining selection procedure of studies of GMV differences.

TABLE 1 | Summary of VBM studies included in the meta-analysis.

References	Diagnosis	No. of CU youth (% male)	Age of CU youth, mean (range)	Quantity of CU by CU youth	No. of TD youth (% male)	Age of TD youth, mean (range)	Quantity of CU by TD youth	Sample	Measures of CU or CUD traits	Time between MR scan and last CU	Comorbidity (% of CU youth with each condition)	Scanner strength (T)	FWHM (mm)	*P*-value	Results
Cousijn et al. (40)	Weekly CU[A]	33 (64%)	21.3 (18.0-25.0)	>10 days per month; 1579.5 (1425.0) joints lifetime use; duration use: 2.5(1.9) years	42 (62%)	21.9 (18.0-25.0)	<50 joints lifetime use	Community	TLFB; CUDIT	24 h abstinent; average abstinence in CU sample: 1.8 (2.3) days	TU (70%)	3.0T	8	ROI mask: $p < 0.005$ Whole Brain: $p < 0.001$, FWE: $p < 0.05$	Group-level analysis Heavy cannabis using adolescents had larger L/R anterior cerebellum volumes compared to Controls, but did not differ from controls in volumes of other brain regions. Correlation analysis Among heavy CU adolescents, amygdala and hippocampal volumes correlated negatively with the amount of cannabis use or problem-severity scores.
Gilman et al. (39)	Weekly ND-CU[B]	20 (45%)	21.3 (18.0-25.0)	>one use per week; 3.8 days/week; 11.2 joints/week; duration use: 6.21(3.43) years	20 (45%)	20.7 (18.0-25.0)	<5 use episodes lifetime; 0 use episodes in past 12 months	Community	TLFB; SCID DSM-IV	Overnight abstinence (> 12 hours)	OTU (70%) DTU (5%)	3.0T	6.9	Bonferroni Correction: ($p < 0.05/4 = 0.0125$)	Group-level analysis For GMV: MJ users had increased nucleus accumbens volumes compared to HC that reached trend-level. For GM density: MJ users had increased GM density in the left nucleus accumbens extending into the subcallosal cortex, hypothalamus, amygdala, and SL-extended amygdala after controlling for age, sex, alcohol use, and cigarette smoking.
Jarvis et al. (42)	BP-CUD[C]	7 (29%)	15 (12.0-18.0)	NR; all with CUD diagnosis; duration use: NP	BP: 7 (43%)	16 (12.0-19.0)	0	Clinical: Inpatient Psychiatric Unit	SCID DSM-IV, ASI, Substance Abuse Course-Modified Life II	NP; > 72 hours abstinent (based upon inpatient setting)	BP (100%)	3.0T	12	$P \leq 0.001$, minimum cluster size 200 voxels	Group-level analyses: BP w/ CUD patients had decreased GMV in left fusiform gyrus and increased GMV in the right caudate and precentral gyrus and increased GM density in the right middle occipital gyrus, right fusiform gyrus, and cerebellar vermis compared to BP w/o CUD patients.
Orr et al. (12)	Low-level CU[D]	46 (65%)	14.6 (14–16)	1-2 instances of CU, lifetime; duration use: < 1 year	46 (48%)	14.5 (14.0-16.0)	0	Community	ESPAD	NP; 13% of CU reported use of cannabis in past 7 days; 22% of CU reported use in past 30 days.	None	3.0T	8	$P <$ 0.001,600 voxel cluster	Group-level analysis Low-level early-adolescent cannabis users had larger volumes in a number of brain regions compared to non-using age-matched controls. Low levels of cannabis use in cohort one was associated with greater gray matter volume in the hippocampus, amygdala, and striatum, bilateral parietal regions, cerebellum, and left middle temporal gyrus. Correlation analysis In addition, the magnitude of differences in GMV were associated with CB1 receptor availability from a separate dataset.

(Continued)

TABLE 1 | Continued

References	Diagnosis	No. of CU youth (% male)	Age of CU youth, mean (range)	Quantity of CU by CU youth	No. of TD youth (% male)	Age of TD youth, mean (range)	Quantity of CU by TD youth	Sample	Measures of CU or CUD traits	Time between MR scan and last CU	Comorbidity (% of CU youth with each condition)	Scanner strength (T)	FWHM (mm)	*P*-value	Results
Thayer et al. (41)	Weekly CU[E]	201 (74%)	16 (14.0-18.0)	>one use per week; 20.6 (9.5) use days in past 30 days; duration use: NP	238 (66%)	16.0 (14.0-18.0	0	Juvenile Justice Involved	TLFB	NP	Alcohol Use	3.0T	6.9	Whole Brain: $P < 0.001$, 1000 voxel cluster	Group-level analysis No group-level differences in GMV were observed between CU and TD youth.
Weiland et al. (11)	Daily CU	50 (82%)	16.7 (14.0-18.0)	Daily use of cannabis; duration use: NP	50 (72%)	16.8 (14.0-18.0)	0	Juvenile Justice Involved	TLFB, past 90 days	NP	Alcohol Use	3.0T	6.9	Clusterwise extent correction: $t > 2.3$, $F > 3.0$	Group-level analysis There was no significant difference in any brain region between cannabis users and controls.

[A]In Cousijn et al. (40), CU participants were heavy CU young adults defined as using cannabis 10 or more days in the month prior to assessment (i.e. > two times per week) and using cannabis on > 240 days over the 2 years prior to assessment. [B]In Gilman et al. (39) – CU participants were defined as weekly or more frequent CU who did not meet DSM-IV criteria for cannabis dependence. [C]In Jarvis et al. (42), all participants were diagnosed with Bipolar Disorder (BP) with CU participants also meeting criteria for DSM-IV diagnosis of current cannabis use disorder (CUD) based upon psychiatric interview (SU module of SCID, DSM-IV). [D]In Orr et al. (12), CU participants were low-frequency users defined as using cannabis on 1 or 2 instances in their lifetime based upon the ESPAD. [E]In Thayer et al. (41) cannabis use was characterized as days of use in past 30 days from the TLFB with days use examined as a predictor of VBM outcomes in a combined sample of CU and non-using youth and in a sample restricted to participants using cannabis weekly or more frequently over the past 30 days. [F]In Weiland et al. (11), CU participants were adolescents who used cannabis on a daily basis over the past 90 days.

ND-CU, Nondependent cannabis users; CU, cannabis users; BP, CUD Bipolar Disorder and CUD comorbidity; SCID (DSM-IV), Substance Use Disorder module of Structural Clinical Interview for Diagnostic and Statistical Manual Mental Disorders, 4th edition; ASI, Addictions Severity Index; ESPAD, European School Survey Project on Alcohol and Drugs; CUDIT, Cannabis Use Disorder Identification Test; TLFB, Timeline Follow Back; TU, Tobacco Users; OTU, Occasional Tobacco User; DTU, Daily Tobacco Users; NP, Not provided.

depicting the search process is presented in **Figure 1** and results from the qualitative analysis (**Supplementary Results S1** and **Supplementary Table S1**) are presented in the supplement.

Study and Sample Characteristics

Six eligible whole-brain VBM studies (11, 12, 39–42) that involved a direct comparison of GMV between CU youth [$n = 357$; mean (SD) age = 16.68 (1.28); age range 14-25 years] and TD youth [$n = 403$; mean (SD) age = 16.77 (1.36); age range 14-25 years] were included in the SDM meta-analysis (**Table 1**). One hundred and five (29.4%) of the 357 CU youth and 151 (37.5%) of the 403 TD youth from the six eligible studies were female. In the meta-analytic sample, the mean ages ($t = 0.01$, $p = 0.99$) and proportion of participants who were of female sex ($t = -0.05$, $p = 0.96$) did not significantly differ across CU and TD groups. One study (42) examined GMV differences between CUD and non-CUD participants with bipolar disorder (BP). All analyses were run with and without this study. Four of six studies controlled for alcohol use in their main analyses and five of six controlled for tobacco use (**Supplementary Table S2**).

Meta-Analysis: Regional GMV Differences in CU vs. TD Youth

The primary SDM meta-analysis (not investigating age or sex) identified no regions showing significant GMV differences between youth with CU compared to TD youth. This null finding remained when analyses were rerun after from a restricted sample excluding the Jarvis et al. study of BP-CUD youth.

Meta-Regression Analysis: Age-Related GMV Effects

Results from the SDM meta-regression examining the effect of age at time of scan on GMV differences between CU and TD youth are shown in **Figure 2**. The age-related meta-regression showed that increasing mean age across adolescence was associated with a relative decrease in GMV in youth with CU vs. age-matched TD youth in the left superior temporal gyrus (L-STG: 85 voxel cluster; MNI peak coordinate: $x = -54$, $y = -4$, $z = -12$; SDM Zmap = −3.168, $p = 0.0008$). This finding remained significant after repeating the main analysis following the removal of a single study in which both CU and TD participants had BP (42).

Meta-Regression Analysis: Sex-Related GMV Effects

Results from the SDM meta-regression examining sex-dependent effects on GMV differences between CU and TD youth are shown in **Figure 3**. The sex-related meta-regression showed that increasing proportion of female participants in studies was associated with a relative increase in GMV in youth with CU compared to sex-matched TD youth in the right middle occipital gyrus (R-MOG: 162 voxel cluster; MNI peak coordinate: $x = 36$, $y = -80$, $z = 28$; SDM Zmap = 3.953, $p = 0.00004$). This finding was no longer significant following the removal of the Jarvis et al. study but remained significant after repeating the main analysis following the removal of each other study.

Supplemental Analyses

As too few whole-brain VBM studies were identified for properly powered subgroup analyses, our planned a priori subgroup analyses were not conducted. Based upon the results from the main analysis which identified a significant age-related and sex-related GMV effects, we chose to still conduct our planned a priori supplemental meta-regression analyses examining the effect of other variables (recent CU frequency, duration of CU, and age range of studies) on GMV. These supplemental analyses are underpowered and should be interpreted as exploratory only. In supplemental meta-regression analyses, increasing duration of CU was associated with a relative decrease in GMV in the L-STG in CU vs. TD youth (**Supplementary Figure S1**: 145 voxel cluster; MNI peak coordinate: $x = -52$, $y = -4$, $z = -14$; SDM Zmap = −3.542, $p = 0.0002$). None of the other assessed variables were significantly associated with GMV differences between CU and TD youth in supplemental meta-regression analyses.

Reliability Analysis

Jackknife sensitivity analysis of the primary meta-analytic results identified no additional significant clusters when studies were sequentially removed from the analysis. Jackknife sensitivity analyses of the meta-regression results (**Supplementary Tables S4, S5**) showed that age-related and sex-related GMV effects were largely preserved through most study combinations. Age-related GMV effects in the L-STG were preserved in four out of six study combinations and the sex-related GMV effects in R-MOG were preserved in five out of six study combinations. The L-STG cluster identified in the supplemental analyses showing GMV differences as a function of duration of CU was observed in four of the six studies (**Supplementary Table S6**).

DISCUSSION

The present meta-analysis investigated age-related and sex-related GMV differences between CU and TD youth to determine the influence of age and sex on reported cannabis-brain morphology relationships across adolescence. To our knowledge this is the first imaging-based meta-analysis of VBM studies of GMV to examine differences between CU and TD youth to specifically investigate for age-related and sex-related effects. The main findings were that CU youth (compared to TD youth) showed GMV differences in temporal and occipital regions that varied as a function of age and sex, respectively. When GMV differences were investigated without examining age or sex effects, no differences were observed between CU and TD youth. Across the six VBM studies included in the meta-analysis, there was significant heterogeneity noted in sample characteristics, comorbidity, and how CU was measured. Implications of these findings are discussed below.

Partially consistent with our hypotheses, we found evidence for age-related GMV differences between CU and TD youth in the L-STG but did not observe differences in other brain regions. This finding suggests that an age/developmental gradient effect

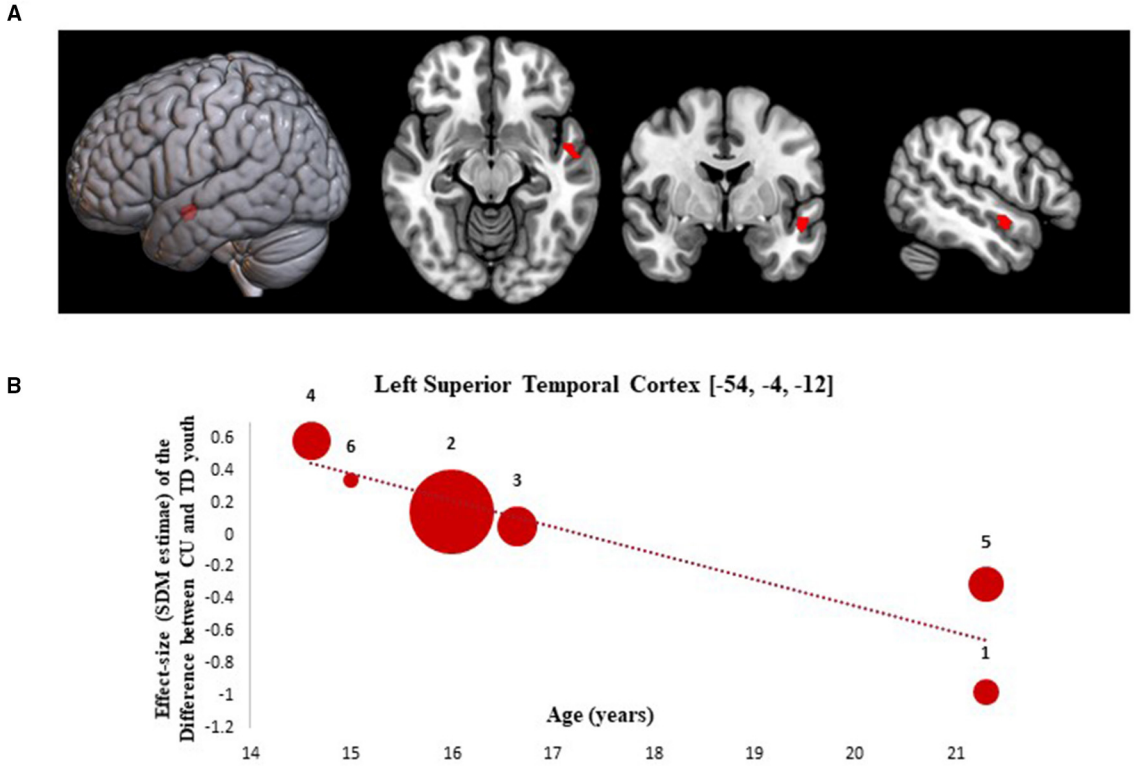

FIGURE 2 | Meta-regression results showing associations between age at scan with gray matter differences between cannabis using and typically developing youth. Age-related meta-regression results. **(A)** Meta-regression results (CU > TD youth) showing associations between Age at Scan and gray matter differences between CU and TD youth shown in red. All results thresholded at $p < 0.005$. **(B)** Associations between age and gray matter differences in the left superior temporal cortex (85 voxels, SDM-Z = −3.168) (shown in red). Effect sizes (SDM-estimates) used to create the meta-regression plots were extracted from the peak of maximum slope significance. The meta-regression SDM-estimate value is derived from the proportion of studies that reported gray matter changes near the voxel so it is expected that some values are at 0 or near +/− 1. Each included study is represented as a numbered dot, with the dot size reflecting relative total sample size of each specific study in comparison to the average total sample size of all six studies included in the regression. Study key: 1 = Gilman et al. (39); 2 = Thayer et al. (41); 3 = Weiland et al. (11); 4 = Orr et al. (12); 5 = Cousijn et al. (40); 6 = Jarvis et al. (42).

of cannabis exposure across adolescence may exist. If true, an age gradient effect could explain some of the divergent results observed across studies. That age-related GMV differences in temporal regions are present in CU youth and decrease as a function of age is consistent with preclinical studies showing non-linear morphologic changes in CB1 receptor enriched brain regions following adolescent cannabis exposure (9, 10). Our results parallel prior human imaging studies showing increased volume and thickness in temporal regions of early-adolescent cannabis users and decreased volumes and thickness in temporal regions of late-adolescent and young adult cannabis users (12, 43, 44). In supplemental analyses, we also identified GMV differences in a L-STG cluster that varied as a function of duration of CU and showed significant overlap with the L-STG cluster identified in our age-related meta-regression analysis. Age and duration of use may be conflated in our analyses, especially as increasing age is associated with increased duration of CU among CU youth. As such, future studies with longitudinal prospective designs, such as the Adolescent Brain Cognitive Development (ABCD) study, are needed to disentangle the relative impact of changes in age and cannabis exposure effects on brain morphology. Our GMV results are consistent with a previous study showing that CUD status influences cortical maturation of the L-STG in adolescents with and without early-onset psychosis (EOP) who were initially scanned at age 16 and then again 18-months later (45). Cannabis exposure starting early and persisting throughout the middle-to-late adolescent periods is associated with greater cortical thinning in PFC regions by young adulthood (46). Moreover, greater duration of CU and higher cumulative cannabis exposure is associated with smaller volumes and thinner cortices in temporal and frontal regions of chronic CU adults who started using in early adolescence (15, 19, 20, 27).

Our findings should be considered within a developmental framework. Adolescence is a critical age range during which extensive cortical thinning and GM reductions occur (47). These morphologic changes are believed to represent normal maturational processes related to synaptic pruning (48). Given this, the age gradient effect hinted at by our results suggests the possibility that divergent structural abnormalities may result from cannabis exposure at different ages (e.g., early adolescence

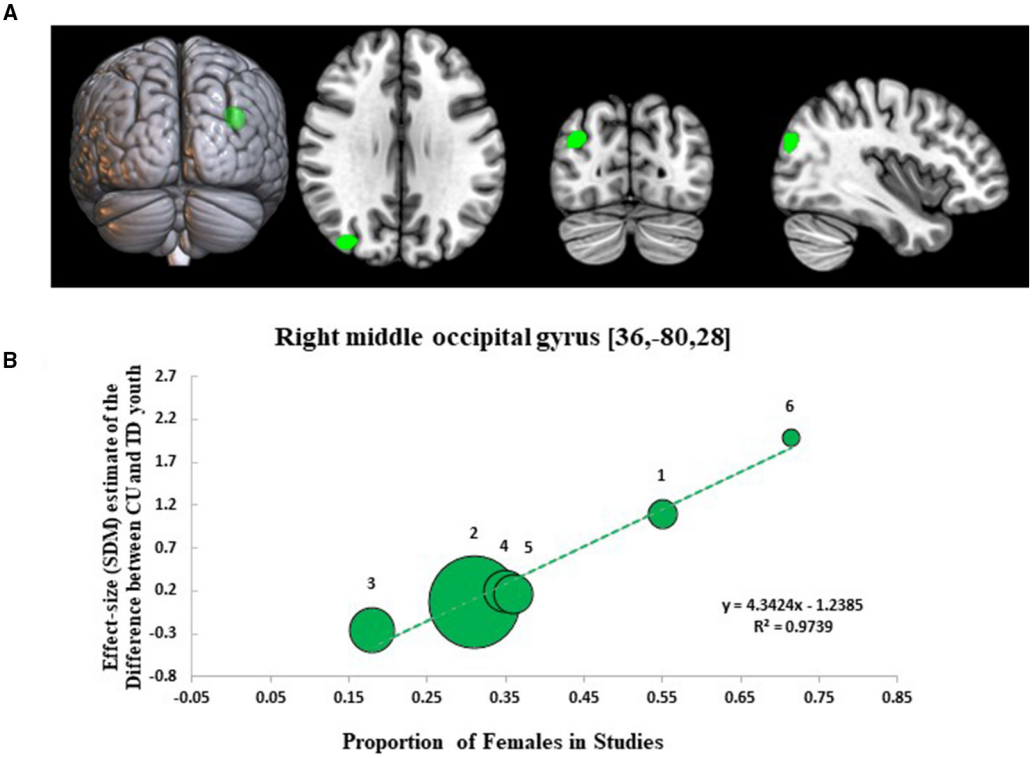

FIGURE 3 | Meta-regression results showing associations between proportion of females in studies with gray matter differences between cannabis using and typically developing youth. Sex-related meta-regression results. **(A)** Meta-regression results (CU > TD youth) showing associations between proportion of females in studies and gray matter differences between CU and TD youth shown in green. All results thresholded at $p < 0.005$. **(B)** Associations between sex and gray matter differences in the right middle occipital gyrus (162 voxels, SDM-Z = 3.953) (shown in green). Effect sizes (SDM-estimates) used to create the meta-regression plots were extracted from the peak of maximum slope significance. The meta-regression SDM-estimate value is derived from the proportion of studies that reported gray matter changes near the voxel so it is expected that some values are at 0 or near +/– 1. Each included study is represented as a numbered dot, with the dot size reflecting relative total sample size of each specific study in comparison to the average total sample size of all six studies included in the regression. Study key: 1 = Gilman et al. (39); 2 = Thayer et al. (41); 3 = Weiland et al. (11); 4 = Orr et al. (12); 5 = Cousijn et al. (40); 6 = Jarvis et al. (42).

vs. young adulthood), and that cumulative cannabinoid exposure may also play a role in cannabis-brain morphology relationships. Further, this gradient could emerge as result of two distinct cannabis-related neuroadaptive/neurotoxic processes that shape cortical morphology in opposing ways at different times during development. For example, in early adolescence, a relative increase in L-STG volume in CU compared TD youth could reflect a disruption in synaptic pruning resulting in the preservation of synapses that would normally be eliminated during refinement of neural circuits (49). In contrast, during late adolescence/young adulthood a relative decrease in L-STG volume in CU compared to TD youth could reflect increased apoptotic mechanisms in specific neuronal cell bodies as a result of cannabis-induced neurotoxicity that occurs when cumulative cannabis exposure has exceeded a certain threshold (9). These developmental hypotheses require additional testing.

Of note, GMV effects related to age and duration of CU from our meta-regressions were both specific to the L-STG, a temporal region involved in auditory, speech, language, face, and emotion processing (50, 51). Temporal brain regions (such as the STG) have increased CB1 receptor expression compared to other cortical regions and thus may be more sensitive to cannabis exposure (33). Our findings are consistent with prior behavioral and functional MRI studies showing evidence of impairments in sensory gating and emotional face processing tasks and altered fMRI blood-oxygen-level-dependent (BOLD) response in the L-STG in CU youth (52–55). The finding also shows relevant overlap with sMRI studies in EOP and schizophrenia (SZD), where reduced gray matter in the L-STG has been observed among individuals with EOP and SZD compared to controls and is associated with increased severity of hallucinations and delusions (56, 57). This may carry clinical significance, especially given the growing literature showing that adolescent CU, especially with high Δ-9-THC potency chemotypes, is associated with increased risk for developing psychotic and affective disorders (58). As such, structural abnormalities in L-STG related to cannabis exposure could lead to impairments in social-cognitive processing, which, in turn could increase the risk for psychotic and affective symptoms in CU youth. Based upon our results, additional research is warranted to investigate the potential role that L-STG abnormalities play in psychosis and negative emotionality of CU youth, as this work may improve our understanding of cannabis's contribution to neurodevelopmental risk factors for psychotic and affective disorders in young people.

One of the main objectives of this study was to investigate the influence of sex distribution on GMV differences between CU and TD youth to determine if any GMV effects are sex-dependent. We identified an occipital cluster centered in the R-MOG that varied between CU and TD youth as a function of sex distribution showing increased GMV in CU compared to TD youth in studies that had a higher proportion of female participants and the opposite relationship (decreased GMV) in studies that had a higher proportion of male participants. This suggests that sex may moderate the relationship between cannabis exposure and occipital morphology during adolescence. Our results regarding sex-related GMV effects are consistent with prior studies in CU adolescents and adults that have shown differences in GMV, cortical thickness, and gyrification in women that are directionally opposition from those found in men (26, 34, 35, 59, 60). A number of possible factors could explain this result. Sex differences in the effect of adolescent cannabis exposure on occipital morphology could result from sexual dimorphism of endocannabinoid system (eCB) tonic signaling (61), CNS signaling pathways (62), hormonal influences (63), or pharmacokinetics (64). Additionally, they could reflect sex differences in brain age at time of cannabis exposure, given that adolescent girls brains are at a more advanced stage of maturation compared to age-matched boys (47). Based upon this, increased R-MOG volume in CU girls relative to sex-matched controls could be related to disruptions in synaptic pruning (49) and decreased R-MOG volume in CU boys could reflect increased sensitivity to cannabis-related neurotoxicity via apoptotic-mechanisms (9). Alternatively, this finding could reflect general neurodevelopmental differences between boys and girls, although this is less likely as sex differences in adolescent brain morphology are less pronounced in occipital regions (65, 66). The sex-related GMV effect could also be the result of differences in cannabis-related behavioral phenotypes between boys and girls who use cannabis. Adolescent boys initiate cannabis earlier than girls, and adolescent girls who use cannabis may have more cannabis-related problems and higher rates of co-occurring/comorbid affective symptoms and disorders, with all of these factors potentially impacting brain morphology (28).

The MOG is involved in visual information processing, attention, and affective and cognitive bias processing (67), which may be dysfunctional in CU individuals (68). Thus, our findings showing sex-related structural abnormalities in the MOG might underlie impairment in these neurocognitive processes and relate to the expression of increased cannabis-related problems and comorbid affective disorders in CU adolescent girls. This interpretation is supported by evidence from previous fMRI studies showing altered BOLD fMRI response in the R-MOG of CU adolescents and adults during visuospatial memory and attentional tasks (69–71) and a previous sMRI study showing cannabis-related changes cortical thickness in the occipital lobe of patients with EOP (56). The result also fits well with fMRI studies reporting alterations in BOLD fMRI response in the MOG and functional connectivity (FC) between the MOG and the thalamus, PFC, and hippocampus in adults with obsessive compulsive disorder (72) and women with depression (73). Moreover, the latter of these two findings points to possible sex differences in relation to MOG activity and connectivity in depressed women. This line of research warrants further study.

Regarding our main findings, it is important to note that our age- and sex-related GMV results showed modest effect sizes and were not replicated in the primary GMV meta-analysis. Given this, it is important to interpret these results cautiously. The age- and sex-related GMV findings could reflect true but subtle differences between CU and TD youth, or alternately could index individual differences in morphology that approximate the range of normal variability which is higher during development (11). Subtle morphological differences related to cannabis exposure, if present, could be obfuscated in studies that are underpowered or have a broad age-range or skewed sex distribution. Problematically, studies in the extant literature without these limitations are rare. Multiple genetic and environmental factors may contribute variance to neuroanatomical abnormalities observed in CU youth. Age- and sex-related GMV differences between CU and TD youth could predate cannabis exposure and be attributed to common predispositional factors, or alternatively could emerge following exposure as a result of cannabis-induced neuroadaptive changes. These explanations are not mutually exclusive. In fact, recent evidence has emerged that partially supports both models [e.g., shared genetic factors (74); premorbid OPFC volumes predicting cannabis initiation in adolescence (75); and cannabis-induced neuroadaptive changes (44, 46)] suggesting complex bidirectional relationships. The ongoing ABCD study should aid in clarifying the nature, directionality, and mediators and moderators of cannabis-brain morphology relationships emerging during adolescence. In addition to the ABCD study, other imaging-treatment studies should also be conducted to address more focal questions about the predictive capacity of neurobehavioral variables on CUD treatment outcomes and the moderating role of sex, age, and other clinical variables (comorbidity, polydrug use) as these types of studies may inform the development of sex-specific treatments and treatment matching algorithms in the future.

This meta-analytic report has a number of important limitations. As the study was a meta-analysis, it was reliant on the study methodology, analytic approaches, and assessments done in each of the VBM studies, few of which were designed or powered to answer specific research questions about age- and sex-related differences in brain morphometry. Based upon study heterogeneity, lack of sufficient information on experimental design and analyses reported by some studies, and the large number of studies using ROI-based analyses, we were limited to making inferences from published coordinates and the number of eligible studies for inclusion in the primary meta-analysis and meta-regressions was small ($n = 6$ studies). As such, our main analyses may have been under powered to detect subtle neuroanatomical differences with small effect sizes and there were insufficient number of studies to conduct appropriately powered subgroup analyses. We sought to address these issues by contacting authors and examining repositories for unthresholded statistical maps with the goal of expanding the number of included studies, but were unsuccessful. Changes in data management and reporting practices, including expectations

for sharing of unthresholded statistical maps or full datasets in online repositories, are needed to support meta-analytic inquiry in this still emerging field. The limited number of studies identified for our meta-analysis also limited our ability to conduct planned sensitivity analyses controlling for alcohol and tobacco co-use. This is problematic, as many CU youth co-use alcohol and tobacco products and recent studies suggest that co-use of cannabis, alcohol, and tobacco may interact and produce unique neuroanatomic and functional abnormalities in poly-users compared to mono-users of these drugs (76, 77). As such, future neuroimaging studies should seek to include poly- and mono-users to dissociate distinct and overlapping effects cannabis, alcohol, and tobacco on brain development in youth. Given the focus on VBM studies, our results are inherently linked to the limitations of this sMRI analytic technique, including its weakness in detecting spatially complex group-level differences such as gyrification and microstructure. Still, it should be noted that our findings overlap with the results from sMRI studies in CU youth and adults measuring cortical thickness, surface area, and microstructural variation (39, 44, 78). Recent studies suggest divergent effects of youth CU on brain and health outcomes as a function of age of cannabis initiation (5, 20). As such, our decision to set the age window broadly (12-21 years) and to include studies with young adult samples could also be viewed as a limitation, although a necessary one, given the small number of whole-brain GMV studies identified for inclusion in the meta-analysis. As observable from **Figure 2**, including youth through age 21 years added variance to the GMV results. This may have obfuscated a main effect of cannabis exposure on GMV, if one was present, but also enabled the examination of GMV effects related to CU as a function of age, sex, and other demographic and clinical variables (which were heterogenous across samples), resulting in the identification of novel age-related and sex-related GMV effects in CU vs. TD youth. Future population-based longitudinal studies should investigate cannabis exposure effects between subjects across narrow age bands (12-14 years, 15-17 years, 18-19 years, 20-21 years) and within subjects over time to identify critical periods of vulnerability to cannabis exposure and to characterize the impact of cannabis exposure across adolescence on brain growth trajectories. Another major limitation is the lack of biochemical quantification of cannabis exposure, and specifically of Δ-9-THC and cannabidiol (CBD) levels, in studies included in this meta-analysis. This limited our ability to investigate this relevant domain. Given preliminary data showing divergent and at times opposing effects of Δ-9-THC and CBD on brain structure and function in adults (79), future studies should measure Δ-9-THC and CBD exposure from cannabis product use and relate these exposures to brain changes in CU youth. Lastly, the majority of studies used in the present meta-analytic report used cross-sectional designs precluding the ability to assign causal determinations. As the field grows and more studies are published using standardized neuroimaging methods and longitudinal designs, quantitative meta-analyses of these studies looking for convergent findings will further inform our understanding of the neurobiological effects of adolescent cannabis exposure. Despite these limitations, the study also has notable strengths. It is one of the first meta-analytic studies to examine neurobiological correlates of adolescent CU. As such, it identifies key targets to guide future research and theory development. Additional strengths include its use of SDM meta-analytic/meta-regression techniques and focus on quantitative assessment of the relationships between age, sex, cannabis exposure, and brain morphology in a developmental sample.

CONCLUSIONS

In conclusion, the results of this meta-analysis suggest that CU youth have significantly reduced GMV in the L-STG and increased GMV in the R-MOG that vary as a function of age and sex, respectively. Duration of cannabis exposure was also associated with reduced L-STG GMV. These findings help to build a more coherent picture of structural alterations in CU youth and how factors such as age and sex influence the presentation of GMV alterations in this population. Our results lend further support to the hypothesis that adolescent cannabis exposure alters brain growth trajectories in subtle ways, and highlights the need for large-scale prospective longitudinal studies to further probe cannabis-brain morphology relationships.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

AA: conceptualization, methodology, investigation, formal analysis, data curation, visualization, writing—original draft, and review and editing. GP: methodology, systematic review, and writing—review and editing. KK: data curation, visualization, and writing—review and editing. MV: visualization and writing—review and editing. KR: methodology, systematic review, data curation, visualization, and writing—review and editing. RL and JN: systematic review methodology, investigation, data collection and curation, and writing—review and editing. CH: conceptualization, methodology, investigation, formal analysis, data curation, writing—original draft, review and editing, and supervision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.745193/full#supplementary-material

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