VERMONT
DEPARTMENT OF HEALTH

Literature review update to the HIA: Marijuana Regulation in Vermont

March 2020

Introduction

This rapid review was undertaken to provide an update to the Health Impact Assessment (HIA): Marijuana Regulation in Vermont. Since the previous update was published in 2017 there has been a substantial increase in the number of articles published related to cannabis and health: 2,203 articles with "marijuana" or "cannabis" and "health" in the title or abstract. Given the time frame available to complete the update the primary focus was review articles and meta-analyses published between January 2017 and February 2020. Primary journal articles were reviewed in some instances to supplement sections (for example, harm reduction) which have not been included in previous versions of either the HIA or the subsequent updates, or there is a paucity of research and consequently few or no review articles. Due to time constraints, not all review articles and meta-analyses were included in this summary and this should not be considered a comprehensive literature review; more recent articles and articles with higher assessed levels of evidence were prioritized, with a total of 132 articles reviewed. There are numerous, systematic, comprehensive resources available that describe the health impacts of marijuana. It is recommended to use these as reference materials.

Suggested references:

- Colorado Department of Public Health & Environment (CDPHE)
  - Based on legislation, the CDPHE is required to provide a summary report every two years of relevant literature related to potential public health effects of marijuana use. A systematic process is used to perform a literature review by a committee of experts. They develop public health statements, evidence statements, public health recommendations, a description of research gaps, a drug interaction table, and a glossary, in addition to their summary report.
- National Academies of Sciences, Engineering, and Medicine (NASEM)
  - The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research (2017)
- WHO Expert Committee on Drug Dependence
  - Critical Review: Cannabis and cannabis resin (2018)
  - The health and social effects of nonmedical cannabis use (2016)

In this update five topics were reviewed in more depth: pregnancy, concentration or potency, harm reduction, effect on driving, and brain development and functioning. The first portion of the document summarizes the general findings related to cannabis and health, and then each topic is summarized. Throughout the document cannabis and marijuana are used interchangeably, reflecting the term of the article's authors. Additionally, while many review articles are cited within this document, for further reference the primary journal articles cited within them should be consulted for further clarification.

Summary of health impacts related to marijuana or cannabis use, by topic

The most comprehensive review of cannabis and the health effects was undertaken in The National Academies of Sciences, Engineering, and Medicine (NASEM) 2017 report, "The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research." A summary of the conclusions from this report were compared to the 2016 WHO report and summarized clearly in the following table (adapted from Table 1 from Cousijun et al., 2018):

Cannabis use-related health effects: conclusions of the National Academies of Sciences, Engineering and Medicine's (NASEM) report compared with the World Health Organization (WHO) report.

NASEM health outcome	NASEM conclusions	WHO conclusion
Therapeutic effects		
Chemotherapy-induced nausea and vomiting	Conclusive evidence for anti-emetic effect, but no good-quality randomized trials	-
Chronic pain	Substantial evidence for modest pain reducing effect	-
Multiple sclerosis	Substantial evidence for moderate reduction of self-reported spasms; limited evidence for effect on clinician-measured spasms; limited evidence for reduction depressive symptoms	-
Sleep problems	Moderate evidence for improvement of short-term sleep outcomes	-
Weight gain and loss	Limited evidence for increasing appetite and decreasing weight loss in HIV; no or insufficient evidence to support or refute treatment effects in anorexia	-
Tourette; social anxiety disorder; post-traumatic stress disorder	Limited evidence for symptom reduction	-
Dementia; glaucoma	Limited evidence that cannabinoids are ineffective	-
Cancer; irritable bowel syndrome; epilepsy; spasticity after paralysis; amyotrophic lateral sclerosis; Huntington's disease; Parkinson; dystonia; addiction; schizophrenia	No or insufficient evidence to support or refute treatment effects	-

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Cancer		
Non-seminoma-type testicular germ cell tumours	Limited evidence for increased risk in cannabis users	Suggestive evidence for increased risk in cannabis smokers
Lung cancer; Head and neck cancers	Moderate evidence for no association	Smoking mix of cannabis and tobacco may increase cancer risks; effect of cannabis alone is unknown
Acute leukaemia; rhabdo-myosarcoma; astrocytoma; neuro-blastoma in offspring	No or insufficient evidence to support or refute associations	
Other cancers	No or insufficient evidence to support or refute associations	
Cardiometabolic risk		
Ischaemic stroke; ubarachnoid haemorrhage; pre-diabetes; acute myocardial infarction	Plausible theoretical link for triggering coronary events; limited evidence for a higher risk of suffering	Some evidence for intoxication triggered coronary events; long-term heavy use potentially triggers myocardial infarctions and strokes in young users
Diabetes; metabolic syndrome	Limited evidence for decreased risk of diabetes and metabolic syndrome; findings are counterintuitive, as THC tends to stimulate appetite, promote fat deposition, and promote adipogenesis	-
Respiratory disease		
bronchitis; respiratory symptoms	Substantial evidence for increased incidences and symptom severity in long-term cannabis users; moderate evidence for improvements in respiratory symptoms after cessation of use	Long-term cannabis smoking causes symptoms of bronchitis and microscopic injury to bronchial lining cells
Pulmonary function	Moderate evidence that acute, but not chronic use, results in bronchodilatation; moderate evidence for higher long volume, but clinical significance is unclear; poor control for tobacco smoking effects	Some studies report higher long function in cannabis smokers
Chronic obstructive pulmonary disease (COPD)	Limited evidence for increased risk in occasional cannabis smokers, controlled for tobacco smoking; insufficient evidence to support or refute associations with COPD severity	No associations

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Asthma	No or insufficient evidence to support or refute associations	-
Immunity		
Immune competence; human immunodeficiency virus (HIV); oral human papilloma virus (HPV)	Animal models and cell cultures support immunosuppressive properties of cannabinoids but insufficient evidence to support or refute effects in healthy humans and humans with HIV and HPV; limited evidence for a decrease in production of several inflammatory cytokines in healthy individuals	-
Viral hepatitis C (VHC)	Limited evidence for no association	-
Injury and death		
Motor vehicle crashes	Substantial evidence for an increased risk	Acute use increases risk of traffic injuries
Cannabis overdose	Moderate evidence for a positive association of increased risk of overdose injuries; insufficient evidence to support or refute a death due to cannabis overdose	-
All-cause mortality; Occupational accidents	Insufficient evidence to support or refute associations	-
Prenatal, perinatal and neonatal exposure		
Maternal cannabis smoking	Substantial evidence for positive association with lower birth weight; limited evidence for association with pregnancy complications; insufficient evidence for negative association with later outcomes in offspring; attribution of outcomes to cannabis exposure is generally problematic	Understudied topic, but offspring demonstrate impaired attention, learning and memory, impulsivity and behavioural problems and a higher likelihood of using cannabis when they mature
Psychosocial		
Cognitive domains of learning, memory and attention	Moderate evidence association cannabis intoxication and impaired functioning; limited evidence for impairments after sustained abstinence	Cannabis intoxication is associated with impaired functioning

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Academic achievement; unemployment and/or low income; social functioning	Limited evidence for a negative association	Daily use in adolescence and young adulthood is associated with early school-leaving
Mental health and substance use		
Cannabis use disorder (CUD)	Substantial evidence that being a male tobacco smoker, frequency of use and early onset of use are risk factors, ADHD stimulant treatment is not a risk factor and CUD severity is higher in males; moderate evidence that depression, being male and polydrug use (but neither alcohol nor nicotine dependence alone) are risk factors; ADHD, anxiety, personality disorders, and bipolar disorders are not risk factors and persistence of CUD is associated with history of psychiatric treatment; limited evidence that childhood anxiety and depression are risk factors; risk factors differ with age: moderate evidence that during adolescence frequency of use, onset of alcohol and nicotine use, oppositional behaviours, parental substance use, poor school performance, antisocial behaviours and childhood sexual abuse are risk factors	The risk to develop a CUD may be 10% in ever users, 17% in adolescent users and 30% in daily users; growing evidence that adolescent heavy cannabis use is associated with more severe outcomes
Other substance use and substance use disorders (SUDs)	Moderate evidence for an association with development of other SUDs (alcohol, tobacco, and other illicit drugs); limited evidence for a higher risk of initiation of tobacco use and higher levels of other illicit substance use	Daily use in adolescence and young adulthood is associated with increased risk of using other illicit drugs
Schizophrenia, psychosis	Substantial evidence for increased dose-dependent risk; a history of cannabis use	Consistent evidence for increased risk, depending on dose, duration and onset

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	may be linked to better cognitive performance in individuals with a psychotic disorder; limited evidence of increased positive symptoms; moderate evidence of no worsening of negative symptoms	age of cannabis use; cannabis use may trigger earlier onset and exacerbated course of the illness
Bipolar disorder	Moderate evidence for that regular user increases symptom severity; limited evidence for increased risk	Existing studies are confounded
Depression	Moderate evidence for small increase in risk; no evidence to support or refute an association with the course of depression	Regular cannabis use during adolescence is associated with increased risk of depressive symptoms
Suicide (ideation, attempts, and completion)	Moderate evidence for increased incidence of ideation and attempts, with higher incidences among heavier users	Daily use in adolescence and young adulthood is associated with increased rates of suicidal ideation
Anxiety	Moderate evidence for increased incidence of social anxiety disorder in regular cannabis users; limited evidence for increased risk to develop any other type of anxiety disorder; limited evidence for increased symptoms severity in near daily users	Comorbidity is evident but not understood
Post-traumatic stress disorder (PTSD)	No evidence to support or refute that cannabis use increased risk; moderate evidence for an association between CUD and PTSD; limited evidence for increased symptom severity among individuals with PTSD	-

Research related to the health impacts of cannabis since the publication of the NASEM and WHO reports has continued at a rapid pace, as cannabis legalization for medical and recreational purposes continues to expand both within the United States and around the world. Significant research gaps and limitations to the past and current research exist. This has often culminated in reviews of topics reporting discordant results, along with lack of sufficient evidence to support associations or causations. To better understand the impact of cannabis use on human health, clearer definitions are needed within research, including frequency of use, cannabis or marijuana THC (and other cannabinoid) content, method of use (i.e., smoking, dabbing, vaping, etc.), and confirmation of use (i.e., self-report, urinalysis, plasma concentration).

Adverse effects of using medical cannabis

Minor adverse effects were commonly reported, including dizziness, dry mouth, nausea, and somnolence or drowsiness, according to the scoping review of systematic reviews (Pratt et al., 2019). Serious adverse effects were less commonly reported, and included psychotic symptoms, seizure, severe dysphoric reactions, and urinary tract infections.

Cancer

Cancer encompasses a wide variety of diseases, so the health impact of cannabis cannot be widely generalized as promoting or inhibiting cancer progression. Based on a systematic review (Rajanahally et al., 2019) of cannabis and male infertility the authors reported there was conflicting data on bladder cancer. However, this review reported anti-neoplastic effects in prostate cancer with cannabis use, but that cannabis use seems to be a risk factor for non-seminomatous germ cell tumors (a type of testicular cancer). Noted limitations in the review include that many studies are in-vitro and animal models, clinical studies do not necessarily agree with the in-vitro and animal models, and many investigations include outdated or anecdotal evidence.

Cannabinoid hyperemesis syndrome (CHS)

Cannabinoid hyperemesis syndrome (CHS) has been difficult to assess due to a lack of consistent diagnostic criteria, according to Venkatesan and colleagues (2019) in their review of chronic cannabis use. The hypothesis posited in this review was that CHS is a subset of cyclic vomiting syndrome (CVS), and chronic cannabis use triggers symptoms in those that are genetically predisposed to CVS. Cannabis is proposed to have anti-emetic (anti-vomiting) effects at lower doses or frequency but can cause vomiting at high doses or sustained use, and there are varying degrees of cannabinoid receptor 1 (CB1) downregulation in chronic users. To support these hypotheses, results from a cross-sectional study of Colorado emergency department visits was included, which reported there was almost twice as many cyclic vomiting cases in the year post marijuana legalization, compared to the year pre-legalization. Similarly, in the post-legalization era there was an 8% yearly increase in hospital discharges for persistent vomiting.

Cooper and Craft (2018) reported in their review of the sex-dependent effects of cannabis and cannabinoids that men were more likely to be diagnosed with CHS than women, but that this may be a reflection of the reported heavier use of cannabis in men compared to women rather than a sex-related sensitivity.

Cannabis use disorder (CUD)

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, (DSM-5), cannabis use disorder must meet two or more of the following criteria within a 12 month period: hazardous use, social/interpersonal problems related to use, neglected major roles to use, legal problems, withdrawal, tolerance, used larger amounts/longer, repeated attempts to quit/control use, much time spent using, physical/psychological problems related to use, activities given up to use, and craving. Cannabis use disorder is proposed to result from a complex interaction of genetic and environmental factors among those who use cannabis. An analysis of US national data using the DSM-5 criteria found 19.5% of lifetime cannabis users met the criteria for CUD (Hasin, 2018). The reported risk of developing CUD was up to 50% greater among daily users and those who began using as an adolescent (Kansagara et al., 2018). There may also be sex-dependent risks for developing CUD: while men are at higher risk for developing CUD, women are increasingly using cannabis and may have increased susceptibility due to "an accelerated progression from initiation of cannabis use to problematic use relative to men, called the 'telescoping effect'" (Cooper and Craft, 2018).

Cardiovascular risks

Congestive heart failure: Cannabis has been independently associated with congestive heart failure based on a study of almost 32,000 patients using cannabis (odds ratio = 1.1; 95% CI 1.03-1.18, $p<0.01$) (Ghosh and Naderi, 2019).

Myocardial infarction: A report on the meta-analysis of 36 studies that evaluated the significant triggers of myocardial infarction (MI) found smoking cannabis to be the third ranking trigger for MI. An epidemiologic study of over two million patients hospitalized for MI found that 35,771 of these patients used cannabis, which translated to an increase risk of MI in cannabis users compared to placebo when adjustments were made for age, gender, other substance use, smoking, and payer status (odds ratio = 1.031, 95% CI 1.018–1.045; $p<0.001$). The authors of the review note that though case reports and retrospective studies suggest there may be negative long-term effects on the cardiovascular system for cannabis users, prospective studies have not indicated a strong association (Ghosh and Naderi, 2019). An additional review assessed that the evidence related to marijuana use and cardiovascular risk factors and outcomes is insufficient (Ravi et al., 2018), which was echoed by DeFelippis et al. (2020).

Arrhythmias: A review article reporting on the retrospective review of almost 2.5 million patients indicated the incidence of arrhythmias in patients who used cannabis nearly doubled from 2010 (1,405) to 2014 (2,252) (Ghosh and Naderi, 2019). Another review article summarized that atrial fibrillation or flutter, atrioventricular block or asystole, sick sinus syndrome, ventricular tachycardia, and Brugada pattern were reported with marijuana use (DeFilippis et al., 2020).

Hemodynamic effects: Contradictory findings reviewed by DeFilippis et al. (2020) led the authors to conclude that the cannabis effects on hemodynamics (blood flow and blood pressure) are uncertain, as is the role of mode of cannabis use in terms of bioavailability related to cardiovascular disease.

Ischemic stroke: Discordant results concerning cannabis use and ischemic stroke among studies have been reported in the review of cannabis and cardiovascular disease by Ghosh and Naderi (2019). A population-based cohort study of over 49,000 Swedish men found no association between cannabis use in young adulthood and stroke. The cohort included men born between 1949-1951, and measured cannabis at only one baseline point between 1968-1970. A retrospective analysis from 2004-2011 National Inpatient Sample (NIS) in the United States found a higher incidence of ischemic stroke in cannabis users compared to non-users (relative risk 1.13, 95% CI 1.11–1.15, p< 0.0001), and a follow up using 2009-2010 data found similar results. From a survey of 2,383 people in Australia between 1999-2002, the rate of stroke or transient ischemic attack (TIA) was 2.3 times higher among cannabis users who used weekly or more often, compared to non-users after adjustment for tobacco and other confounders (95% CI 1.1–4.5). Additionally, a population study mentioned in the DeFilippis et al. (2020) review found marijuana use in the past year led to an increased rate (3.3x) of cerebrovascular events (stroke).

The Coronary Artery Risk Development in Young Adults (CARDIA) longitudinal cohort study did not find an association between lifetime or recent cannabis use and cardiovascular events. This study included 5,115 young adults, ages 18-30, beginning in 1985-86 with follow up for a mean of almost 27 years. Outcomes examined in the study included cardiovascular disease, cardiovascular mortality, and stroke. This was the largest prospective study that examined the association and did not find there was an association between lifetime or recent cannabis use and cardiovascular events (Ravi et al., 2018).

Death

In Hasin's review of the epidemiology of cannabis use in the US and the associated problems (2018) there were no causes of fatal overdose due to cannabis in the epidemiologic literature. Cannabis use has been associated with fatal driving and aviation injuries.

Diabetes

A review of the effects of cannabis use in youth in young adults with Type 1 Diabetes (T1D) (Pancer and Dasgupta, 2019) assessed there to be a dearth of sufficient studies related to the topic, with the studies available mostly relying on self-report and cross-sectional assessment. From the limited evidence, it was reported that cannabis use may be associated with higher glycated hemoglobin and greater incidence of diabetic ketoacidosis. There were no statistically significant differences observed between user and non-users of cannabis in rates of severe hypoglycemia. While animal models suggest cannabis may be protective against T1D, these findings have not been replicated in humans. A separate review (DeFilippis et al., 2020) mentions a small, randomized, double-blind, placebo-controlled, parallel group pilot study in patients with Type 2 Diabetes (T2D). This study examined the efficacy and safety of cannabidiol (CBD) and Δ (9)-tetrahydrocannabivarin (THCV), a non-psychoactive compound found in cannabis. THCV treatment significantly decreased fasting plasma glucose levels and improve pancreatic β-cell function.

Erectile dysfunction (ED) and male fertility

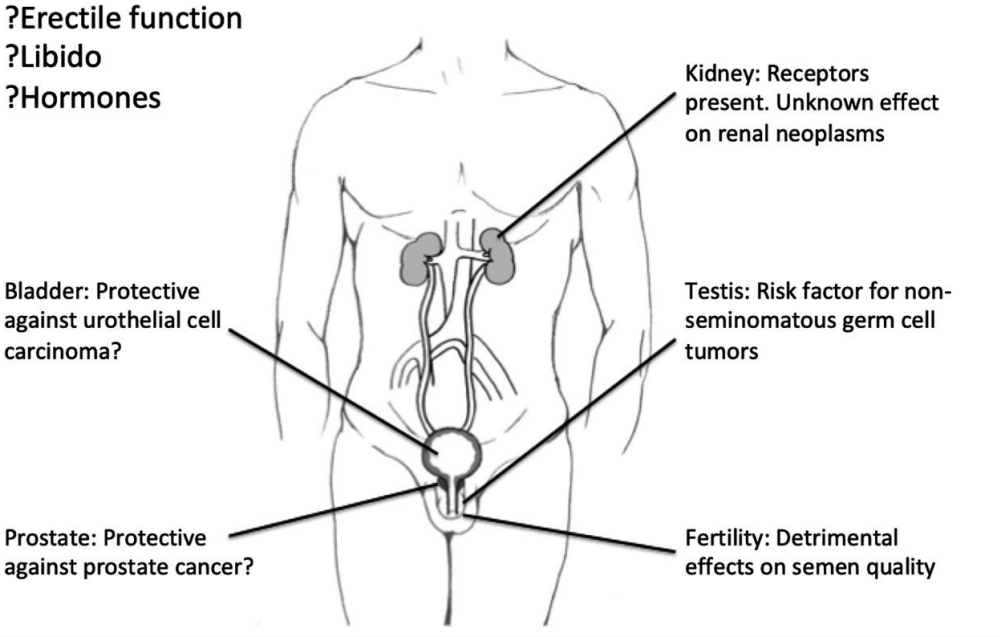
A review and meta-analysis (Pizzol et al., 2019) combined five case-control studies to assess the relationship between erectile dysfunction (ED) and cannabis use. The prevalence of ED in cannabis users was 69.1% (95% CI: 38.0–89.1) and non-users was 34.7% (95% CI: 20.3–52.7), with a calculated odds ratio of ED in cannabis users nearly four times that of controls (odds ratio = 3.83; 95% CI: 1.30–11.28; p = .02). However, there was very high heterogeneity (I^2= 90%). The authors concluded that ED is twice as high in cannabis users compared to controls. However, the authors mention that by utilizing case-control studies the directionality of the relationship cannot be established and reverse causality is a possibility: those with ED used cannabis more often. A separate review examining the relationship between cannabis and male infertility, sexual health, and neoplasm (Rajanahally et al., 2019) suggests there may be a dose-dependent relationship of cannabis use that contributes to ED. Additionally, they suggest cannabis use contributes to detrimental effects on semen quality. They summarized their results in the following table and infographic:

Table 1 Summary of clinical studies on marijuana and male infertility

Author, Year	Type of study	Level of evidence	Subjects	Relationship to fertility?
Hembree *et al.* (1978)	Multiple-baseline design	NA	16	Yes. Decrease in motility, concentration, total sperm count, and normal morphology
Close *et al.* (1990)	Case–control	IV	164	No, although there was an increase in seminal leukocytes
Amoako *et al.* (2014)	Case–control	IV	90	Yes. Decrease in motility and viability
Lewis *et al.* (2012)	Cohort	IV	150	Yes. Reduction in endocannabinoid levels in infertile seminal plasma paralleled by increased degradation:biosynthesis ratios
Amoako *et al.* (2013b)	Cross sectional	VI	86	Yes. Reduction in endocannabinoid levels in men with abnormal semen analyses
Pacey *et al.* (2014)	Case–control	IV	318	Yes. Decreased normal morphology
Gundersen *et al.* (2015)	Cohort	IV	1215	Yes. Decreased concentration and total sperm count

NA, not applicable.

Figure 2 Current understanding of the effects of cannabis on male infertility, sexual health, hormonal health, and urologic neoplasms.



Eyelids

A comprehensive review (Nguyen and Wu, 2019) examined the association between cannabis and eyelids did not find conclusive evidence to explain the relationship between cannabinoids and eyelid tremors. Their findings suggested that cannabis could potentially treat blepharospasm (eyelid spasm) but that cannabis use has also been associated with eyelid tremors and significant ptosis (drooping of upper eyelid).

Kidney function

Effects of cannabis on the endocannabinoid system related to kidney function is not yet well understood, as summarized by Ho et al. (2019). From what is known, the authors emphasized that cannabis use has not been associated with a loss of kidney function. Consequently, they recommend non-synthetic cannabinoids should be limited to use for chronic kidney disease (CKD) to treat chronic neuropathic pain. Use of topical treatments for uremia-induced pruritus (common in end-stage renal disease) is promising but lacks sufficient supporting evidence. Using cannabis for pain management is echoed by Rein's (2020) review, recommending the lowest effective non-smoking dose be used for CKD and end-stage renal disease (ESRD), and renal function to be continuously monitored. However, cannabis use could potentially delay or contribute to ineligibility for kidney transplant due to institutional restrictions.

Lung function

A systematic review and meta-analysis (Ghasemiesfe et al., 2018) suggested there is insufficient evidence for the association between daily marijuana use and obstructive lung disease and impaired pulmonary function. Their results indicate that among marijuana users (of more than once per week for a minimum of a year) there was low-strength evidence that associated smoking with cough, sputum production, and wheezing. Others have reported chronic airway inflammation and epithelial injury (basal cell hyperplasia, goblet cell hyperplasia, subepithelial inflammation) with long-term marijuana use. Kansagara and colleagues (2019) also mention an observed decline in lung function over the course of decades long daily cannabis smoking, along with an association with symptoms of chronic bronchitis. Hasin's review (2018) indicates that co-use of cannabis and tobacco present a greater risk of respiratory distress than either substance individually.

Medication interaction

Cox et al. (2019) report there are substantive deficiencies in pharmacokinetic data to completely characterize potential drug interactions with marijuana. The authors report there are likely some 500 chemical constituents in the marijuana plant, and there are ten major subtypes of phytocannabinoids (cannabinoids derived from plant material). They summarize that cannabinoids generally interact with the body through two cannabinoid receptors: CB1 (found in both the central and peripheral nervous systems) and CB2 (found primarily in the peripheral nervous system, especially the spleen and thymus). It is reported (DeFilippis et al., 2020) that cannabinoids are known to affect classes of cardiovascular medications: antiarrhythmics, calcium-channel blockers, statins, beta-blockers, and warfarin. Additionally, potential drug interactions with cytochrome P450 isoenzymes was raised as an issue of concern for cannabis treatment and potential adverse effects in patients with hepatic (liver) impairment (Ho et al., 2019).

Metabolic effects

A review (Ravi et al., 2018) summarized conclusions from cross-sectional studies which suggested metabolic benefits of using marijuana. However, studies with stronger analytic designs did not agree, and prospective studies concluded there were potentially harmful effects. Additionally, there have been discordant results for marijuana contributing to weight gain or loss (DeFilippis et al., 2020).

Mental Health

A systematic review and meta-analysis (Black et al., 2019) concluded there is a lack of evidence to suggest cannabis use improves depressive disorders and symptoms, anxiety disorders, attention-deficit hyperactivity disorder (ADHD), Tourette syndrome, post-traumatic stress disorder, or psychosis.

Anxiety: As analyzed by Gobbi and colleagues (2019) in their systematic review and meta-analysis comprising over 23,000 people, the authors conclude there is not an association between cannabis consumption and anxiety. In contrast, Esmaeelzadeh and colleagues (2018) identified a significant association between anxiety and cannabis use among adolescents and young adults (odds ratio= 1.36, 95% CI: 1.02–1.81) in their systematic review and meta-analysis. The relationship between cannabis use and anxiety symptoms is supported by epidemiological evidence (Sarris et al., 2020).

Bipolar disorder: Pinto and colleagues (2019) in their systematic review, meta-analysis, and meta-regression examined the prevalence and clinical correlates of cannabis use and cannabis use disorder (CUD) among patients with bipolar disorder. The authors report cannabis use and CUD were highly prevalent in the clinical and population samples of people with bipolar disorder (24%) compared to the general population estimate (2-7%). They concluded that patients with bipolar disorder who used cannabis were more likely to have lifetime psychotic symptoms, which they associated with poorer clinical outcomes (suicide) and functioning. Additionally, there was an increased chance of presenting with lifetime misuse of alcohol, nicotine, and other psychoactive substances. However, there were no calculated differences in other variables associated with bipolar disorder progression and cognitive impairments (i.e., rapid cycling, co-morbid anxiety disorders). Demographically, cannabis use among bipolar disorder patients was associated with males, being single, and fewer years of education.

Depression: A systematic review and meta-analysis of over 23,000 people across eleven studies concluded adolescent cannabis consumption was associated with an increased risk of developing depression (odds ratio = 1.37, 95%CI, 1.16-1.62; I^2 = 0%) when compared to nonusers. This association was observed to be unidirectional, with cannabis use resulting in depression (OR = 1.33, CI = 1.19–1.49) (Gobbi et al., 2019). Pooled results from another systematic review and meta-analysis (Esmaeelzadeh et al., 2018) calculated a positive association between depression and cannabis use in adolescents and young adults (OR = 1.29, 95% CI: 1.10-1.51). This observational data is supported by genetic studies, which suggest either common reasons underlying the comorbidity with CUD and major depression, or CUD as a causative agent of major depression (Hasin, 2018). Sarris and colleagues (2020) suggest higher doses of cannabis used could increase depressive symptoms.

Post-traumatic stress disorder (PTSD): There was weak evidence for improving post-traumatic stress disorder according to Sarris and colleagues clinically-focused systematic review (2020).

Psychosis: Cannabis use has been associated with an earlier onset of psychosis, along with an increased risk of transition in those at clinical high risk of psychosis, according to van der Steur and colleagues (2020) in their systematic review of factors moderating the association between psychosis risk and cannabis use. Additionally, frequent use of high potency cannabis (high THC to CBD ratio) has been associated with higher risk of psychosis development. They report that the majority of studies from the past ten years have concluded that cannabis use is associated with an earlier onset of psychotic symptoms, experiences, or psychotic disorder. Memedovich and colleagues (2018) reported cannabis use was associated with earlier onset of psychosis, and cannabis use or abuse was associated with the transition to psychosis among those at "ultra-high risk" for psychosis, both compared to no cannabis use. According to the authors (van der Steur et al., 2020), there are several genotypes that moderate the effect of cannabis use on the risk of psychosis, particularly those involved in dopamine function (i.e., AKT1). Studies evaluating the relationship between age of initiation of cannabis use and psychosis suggest cannabis use at an early age alone is insufficient to precipitate psychotic illness, as cannabis use is only part of a system of genetics and environmental factors that can produce psychosis (Hosseini and Oremus, 2019).

Schizophrenia: A systematic review (Sarris et al., 2020) suggested longitudinal data supports a causal relationship between cannabis use and schizophrenia. More specifically, heavy cannabis use may lead to a schizophrenia diagnosis. It is reported that there is a strong relationship between recent or current use among ultra-high-risk adolescents with cannabis use disorder. Additionally, schizophrenia risk alleles have been associated with cannabis use in the general population. An increased risk of schizophrenia and psychotic symptoms was associated with heavy, average, ever, more frequent, and early cannabis use compared to never use was reported [(heavy OR 3.90, 95% CI 2.84-5.34), (average OR 1.97, 95% CI 1.68-2.31), (ever OR 1.41, 95% CI 1.20-1.65), (more frequent OR 2.09, 95% CI 1.54-2.84), (early use OR 2.90, 95% CI 2.40-3.60)] (Memedovich et al., 2018). Another review (Hamilton and Monaghan, 2019) concludes there is not yet sufficient evidence to establish cannabis use as causation for development of schizophrenia.

Suicide: A systematic review and meta-analysis of over 23,000 individuals concluded that adolescent cannabis use was associated with suicidal ideation (pooled OR 1.50, 95% CI 1.11-2.03, I^2 = 0%) and suicide attempt later in life (pooled OR 3.46, 95% CI 1.53-7.84, I^2 = 61.3%) (Gobbi et al., 2019).

Oral health

Li and colleagues' review (2019) found cannabis use was associated primarily with an increase in the incidence of dental caries. Poor oral hygiene, higher plaque scores, and less saliva production were reported as factors that contributed to the dental caries. The relationship with periodontal disease and cannabis was characterized as less clear due to conflicting findings, but chronic inflammation, leukoedema, and dysplasia seem to be more common among cannabis users. A systematic review examining cannabis inhalation and voice disorders concluded cannabis inhalation was associated with dark vocal folds, and smoking was associated with lung and throat injuries (Meehan-Atrash et al., 2019).

Sleep

A review of clinical trials related to cannabinoids and sleep (Kuhathasan et al., 2019) concluded THC and THC-derivatives may improve self-reported sleep. The authors noted a lack of placebo-controlled trials that studied sleep disorders and noted the majority of studies reviewed only examined sleep as a secondary outcome, often with non-validated, non-standardized questionnaires.

Tuberculosis (TB)

A systematic review assessing cannabis use and the risk of tuberculosis (TB) concluded there was weak evidence for an association between cannabis use and TB (French et al., 2019).

Ulcerative colitis (UC)

A review of randomized controlled trials in adults comparing cannabis or cannabinoid derivatives to placebo or an active therapy concluded the effects of cannabis on ulcerative colitis (UC) are uncertain. Additionally, there was no evidence to support using cannabis for maintenance or remission in UC (Kafil et al., 2018).

Withdrawal

Cannabis withdrawal is defined in the Diagnostic and Statistical Manual, 5th edition, (DSM-5) as a syndrome with three or more of the following symptoms after cessation of prolonged cannabis use: anxiety, restlessness; depression, irritability; insomnia/odd dreams; physical symptoms, e.g. tremors; and decreased appetite (Hasin, 2018). Symptoms can develop up to one week after cessation and can last for up to several weeks (Kansagara et al., 2019). Cannabis withdrawal has been reported by up to one-third of those considered as "regular users" in the general population, and between 50-90% of those considered as "heavy users" in treatment or research studies, and seems to have pharmacological specificity (Hasin, 2018). Among heavy users, withdrawal symptoms have been observed during conventional hemodialysis (Ho et al., 2019). Interestingly, cannabis withdrawal symptoms overlap with reasons reported for cannabis use. Thus, Kansagara and colleagues (2019) suggest it is important for the public and health care providers to be aware of cannabis withdrawal syndrome. They suggest the clinical significance of this syndrome is supported by the evidence that it can be impairing, cannabis and/or other substances are used to treat or relieve it, and the association with difficulty in cessation and associated worse treatment outcomes.

Sex-related differences have been reported, with women experiencing worse outcomes relative to men, such as severity of craving, ability to achieve abstinence, and withdrawal symptoms. This is reported to be consistent with daily, smoking, women users with, "increases in subjective effects that reflect abuse liability, and deficits in neurobiological markers associated with addiction severity" (Cooper and Craft, 2018).

Potential additional risks

Cannabis testing is considered to be in its infancy according to Atapattu and Johnson (2019). There are not widely accepted conventions for the scope of required testing, pesticide limits, or regulatory requirements for pesticides in the United States (US). Resultantly, there is variation by region within the US, and regulations are generally less strict than in Canada. Contaminants within cannabis or cannabis products can be hazardous to health. Pesticide contaminates, or the

products produced by heating or burning, can produce toxic materials. Toxic materials can also be produced when the pesticides, or their heated or burned products, interact with the cannabis itself when heated or burned.

Marijuana use and pregnancy

Prevalence and frequency of marijuana use during pregnancy

A review (Ryan et al.,2018) suggests marijuana is one of the most widely used substances during pregnancy in the United States. The authors report data from the 2016 National Survey on Drug Use and Health (NSDUH) in which 4.9% of pregnant women aged 15 through 44 years of age reported use of marijuana in the past month.

A recent review (Singh et al., 2020), reviewed forty-one studies on pregnancy and marijuana use. The authors reported prevalence of prenatal cannabis use across the studies ranged from 0.24% to 22.6%. Three of the studies included in the review reported increases in the prevalence of prenatal cannabis over time.

A recent article (Alshaarawy and Anthony, 2019) also reported increases in prevalence over time by pregnant women, specifically in the first trimester of pregnancy. Use in the first trimester increased from 5.6% between 2002-2005 to 8.1% between 2014-2017.

An article (Skelton et al., 2020) assessed prenatal marijuana use using the Pregnancy Risk Assessment Monitoring System (PRAMS) data and compared prevalence between states with and without legalized recreational cannabis. Adjusted analyses found in states with legal recreational marijuana women were more likely to use marijuana during preconception, prenatal and postpartum periods compared to states without legal recreational use.

A recent article (Young-Wolff et al., 2019) assessed frequency of use of marijuana from 2009 to 2017. The authors report more rapid increases in daily use compared to rates of weekly or monthly use.

It is important to note most studies of marijuana use during pregnancy assess use with self-reported questionnaires. One study (Young-Wolff et al., 2019a) measured the validity of self-reported cannabis use among pregnant women in northern California. Urine toxicology testing was used to confirm marijuana use or detect previously unreported marijuana use. Urine toxicology testing identified more instances of prenatal cannabis use than self-report (4.9% vs 2.5%), highlighting that the sensitivity of self-report was low (33.9%). This suggests self-reported marijuana use is not an accurate measurement of actual marijuana use, and consequently using self-report likely underestimates actual use during pregnancy.

Marijuana and other substance use during pregnancy

An article (Qato et al., 2019) assessed the most common co-use combinations among pregnant women involved marijuana, tobacco, and alcohol. Marijuana was reported as frequent among co-use patterns, with marijuana involved in 6 of the 10 most prevalent co-use patterns.

Additionally, a retrospective cohort study of marijuana-exposed pregnancies identified that marijuana exposed pregnancies were significantly more likely to also report tobacco use during pregnancy compared to pregnancies without marijuana exposure. Other illicit drug use was not statistically significantly different by marijuana exposure status (Rodriguez et al.,2019).

Marijuana use and in utero effects during pregnancy

The psychoactive component of most marijuana compounds, delta-9-tetrahydrocannabinol (THC), enters maternal circulation and readily crosses the placental membrane (Cecconi et al., 2019). As a result, concerns have been raised about the potential effects of in utero exposure to THC from marijuana use. Longitudinal studies evaluating long-term consequences of prenatal exposure(s) have yielded inconsistent conclusions.

The effect of marijuana use or THC on placental and fetal development focus mainly on the endocannabinoid signaling system. A recent article (Almada et al., 2020) suggested marijuana use during pregnancy may affect placental development directly, or indirectly by disrupting the homeostasis of the endocannabinoid system. The endocannabinoid system is complex and is still under preliminary research.

A review (Franks et al., 2019) assessed prenatal drug exposure and glucocorticoid signaling, with their finding summarized in the below figure. The authors concluded prenatal substance exposure (including marijuana) triggers a stress response which could impact fetal neurodevelopment.

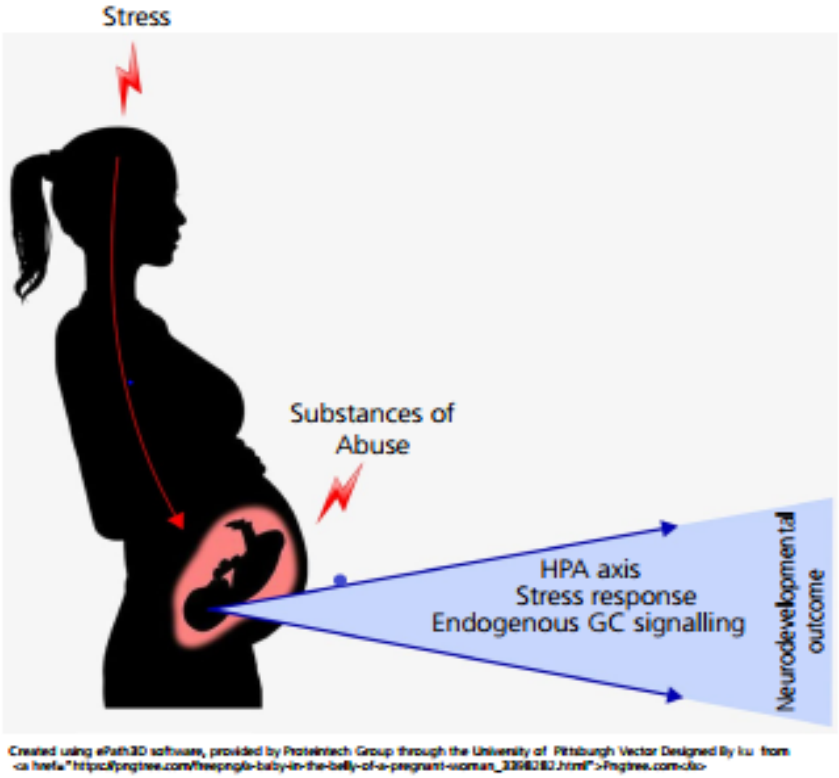


FIGURE 1 Prenatal exposure to stress and substances of abuse impact neurodevelopmental outcome. Following prenatal exposure to stress and/or teratogenic agents, multiple points of interaction converge to influence endogenous glucocorticoid (GC) signalling, hypothalamic/pituitary/adrenal (HPA) axis regulation and the stress response. Ultimately, these may result in developmental abnormalities that persist into adulthood

Almada and colleagues assessed the effect of THC on placental cell proliferation in vitro and concluded THC can decrease cell viability and induce apoptosis of placental cells at high concentrations (Almada et al., 2020).

Physical health outcomes of marijuana use during pregnancy

A review (Marroun et al., 2018) discussed that children exposed to cannabis in utero have lower birth weight and are more likely to need placement in the neonatal intensive care unit (NICU). However, the authors did not identify differences in outcomes such as still birth, neonatal length, or head circumference.

The American Academy of Pediatrics published a clinical report in 2018 which discussed the implications of neonatal and childhood outcomes associated with marijuana use during pregnancy. The authors reiterate the results of previous reviews, which have suggested an association with low birth weight and NICU placement. The authors also discussed an older meta-analysis by Conner et al., in 2016 which reviewed 31 studies relating the effects of marijuana exposure during pregnancy and neonatal outcomes including low birth weight, preterm delivery, birth weight, gestational age at delivery, admission to the NICU, still birth, spontaneous abortion, low Apgar scores, and placental abruption. The meta-analysis found women who smoked marijuana were at risk for preterm delivery, lower birthweight, lower APGAR scores, and stillbirth. There was no independent relationship identified between marijuana use and small for gestational age status, placental abruption, need for NICU admission, or spontaneous abortion. The authors of the clinical report noted this meta-analysis had a major strength of including cohort studies which adjust for the common confounders of use of other substances and socioeconomic status.

A review (Cook et al., 2017) summarized the effect on high-dose marijuana use during pregnancy. High-dose marijuana use was linked to effects associated with low birth weight, incidence of tremors, exaggerated startles, and diminished crying.

A recent review (Thompson et al., 2019) did not find evidence of an association between stillbirth or early miscarriage and marijuana exposure. The authors reviewed evidence of preterm labor and preterm birth. One large systematic review found a decrease in gestational age and increased odds of preterm delivery. Two other studies also noted an increased risk of spontaneous preterm birth. This review article mentions several studies have found associations with marijuana use and decreases in birth weight, but no significant association with head circumference or length. Lastly, the review article assessed risk of NICU admissions, and included the results of two studies which found a significant association with NICU admission and prenatal marijuana use.

Another recent review (Singh et al., 2019) focused on prenatal recreational marijuana use in high-income countries. The authors provided a summary table with adjusted odds ratios (ORs) and confidence intervals (CI) of the risk of low birth weight, neonatal intensive care unit admission, preterm birth, and small for gestational age (see the following table, adapted from Singh et al., 2019 “Table 2. Neonatal health outcomes of prenatal recreational cannabis use”). While not all studies were in agreement, the overarching theme was marijuana use was associated with more negative health outcomes for neonates.

Neonatal health outcomes of prenatal recreational cannabis use

Study (year of publication)	Adjusted Odds Ratio (Relative Risk)	95% Confidence Interval
Low Birthweight		
Reichman & Teitler (2003)	1.05	Not reported
Campbell et al. (2018)	2.72	1.67-4.43
Hayatbaksh et al. (2012)	1.70	1.3-2.2
Bada et al. (2005)	1.21	0.9-1.61
Conner et al. (2015)	1.30	0.91-1.8
Van Gelder et al. (2010)	0.70	0.3-1.6
Crume et al. (2018)	1.50	1.1-2.1
Neonatal intensive care unit admission		
Corsi et al. (2019)	1.40	1.36-1.44
Burns et al. (2006)	2.00	1.7-2.5
Hayatbaksh et al. (2012)	2.00	1.7-2.4
Conner et al. (2015)	1.60	0.7-3.5
Warshak et al. (2015)	1.54	1.14-2.07
Crume et al. (2018)	1.00	0.6-1.7
Preterm birth		
Corsi et al. (2019)	1.41	1.36-1.47
Burns et al. (2006)	2.20	1.9-2.5
Hayatbaksh et al. (2012)	1.50	1.1-1.9
Saurel-Cubizolles et al. (2014)	1.24	0.44-3.49
Chabarria et al. (2016)	0.84	0.35-3.87
Bada et al. (2005)	0.90	0.73-1.11
Warshak et al. (2015)	1.09	0.89-1.33
Van Gelder et al. (2010)	1.00	0.6-1.9
Crume et al. (2018)	1.30	0.8-2.1
Small for gestational age (SGA)		
Corsi et al. (2019)	1.41	1.36-1.45
Burns et al. (2006)	2.00	1.7-2.2
Luke et al. (2019)	1.47	1.33-1.61
Hayatbaksh et al. (2012)	2.20	1.8-2.7
Saurel-Cubizolles et al. (2014)	1.24	0.52-2.94
Bada et al. (2005)	1.08	0.85-1.36
Warshak et al. (2015)	1.30	1.03-1.62
Leemaqz et al. (2016)	1.84	0.90-3.76
Crume et al. (2018)	1.30	0.8-2.2
Smith et al. (2006)	0.68	0.30-1.54

Kharbanda and colleagues (2019) assessed prenatal marijuana use and adverse birth outcomes including SGA, low birth weight, and major structural birth defects. A major strength of the study was the use of urine toxicology testing to identify marijuana-exposed infants and adjusted analyses for common confounders including smoking. The authors calculated an adjusted relative risk of 1.42 (95% CI:1.22-2.34) for SGA births among mothers who used marijuana. Of note, the addition of smoking increased the adjusted relative risk to 2.38 (95% CI 1.35-4.19), which suggested use of both substances increased the likelihood of negative health outcomes.

Stein and colleagues (2019) examined infants exposed to concomitant opioid and marijuana use. After adjusting for maternal and infant characteristics, infants exposed to marijuana and opioids had increased odds of preterm birth (adjusted odds ratio 1.72, CI 1.33-2.22) and low birth weight (adjusted odds ratio 1.46, 95% CI 1.13-1.87) compared to those with opioid exposure alone. Infants exposed to both marijuana and opioids had decreased odds of neonatal abstinence syndrome (NAS) and hospital stays, compared to infants with opioid exposure without marijuana use.

Rodriguez and colleagues (2019) assessed prenatal cannabis use and neonatal health outcomes in Colorado, which has legalized both medial and recreational use of marijuana. The sample of marijuana-exposed infants was small (n=211) but there were statistically significant associations with small for gestational age and smaller head circumference in multivariable modelling.

Developmental and neurocognitive outcomes associated with marijuana use during pregnancy

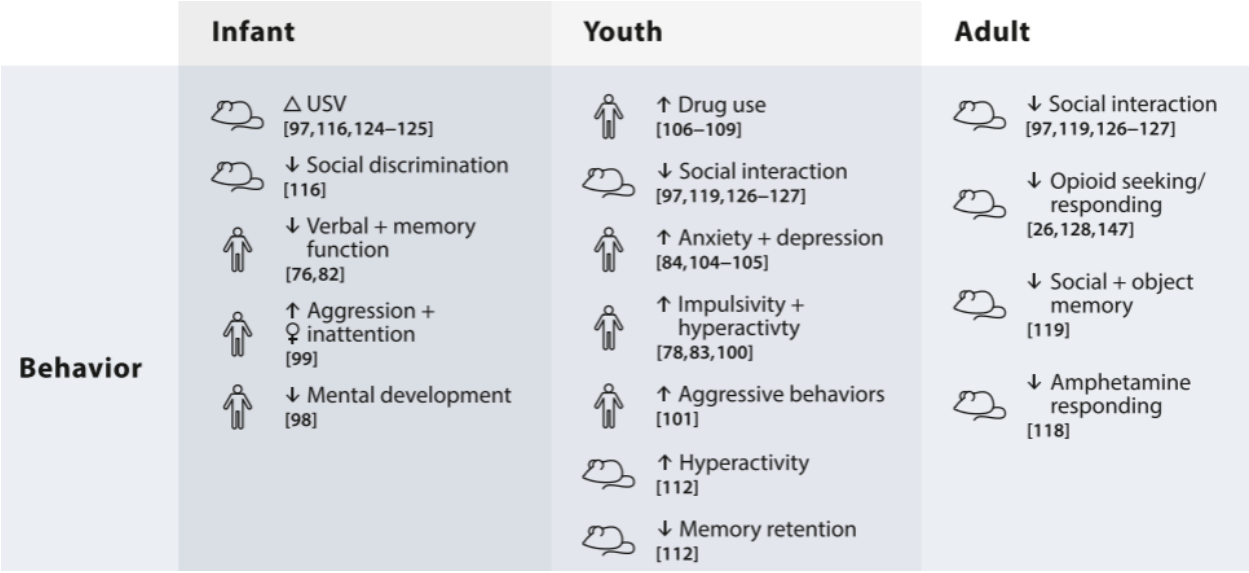
A review by Cook and colleagues (2017) summarized the effects of marijuana use during pregnancy and long-term neurocognitive outcomes. The authors suggested effects of marijuana use may be dose dependent and there may be an association with memory, verbal, visual reasoning impulsivity, attention issues, and aggression.

A review (Sharapova et al., 2018) assessed long-term neuropsychological outcomes of children aged 1-11 who had been prenatally exposed to marijuana. There were discordant results from the twenty-one studies assessed. However, there were more negative associations with children exposed to marijuana in utero.

A recent review article (Guille and Aujla, 2019) assessed developmental consequences of prenatal substance use in children and adolescents. The authors discussed several prospective cohort studies which suggest an association with negative effects on executive and intellectual function among school-age children and adolescents. Of note, the authors highlight important limitations in some of the studies such as residual confounding, appropriate control groups, and environmental factors which cannot be controlled for.

Carlier and colleagues (2019) summarized in their review several recent articles on the relationship between perinatal marijuana exposure and long-term cognitive effects. The results between the studies are discordant and suggest any statistically significant results may not be related to perinatal drug exposure, but due to confounding factors such as epigenetics or parental behavior.

A review (Scheyer et al., 2019) assessed the consequences of perinatal marijuana exposure. The authors highlighted that there were only three longitudinal studies focused on behavioral outcomes, which are older. The assessed limitations were differences in frequency and potency of marijuana, genetic/environmental contributions, and only two of the three studies had long-term follow-up data. The findings are summarized in the adapted figure below (adapted from Scheyer et al., 2019 "Figure 3. Consequences of Perinatal Cannabis Exposure in Humans and Rodents").



Summary and recommendations

The prevalence of marijuana use during pregnancy has increased. Research suggests THC crosses the placental membrane and therefore could affect the fetus in utero. However, the research on the effects of marijuana use in pregnancy is limited, and results discordant, but overall the research tends to suggest marijuana use results in negative outcomes. Many of the articles cite the increased potency of THC in marijuana that is now available as a concern, as there is the potential of an increase in THC resulting in more negative effects. Further research is needed to assess effects of marijuana use in pregnancy related to in utero development, neonatal outcomes, and long-term effects. As a result, the American College of Obstetricians and Gynecologists recommends pregnant women do not use marijuana during pregnancy.

Brain functioning and development

A discussion of the behaviors associated with the impacts of cannabis use on neurocognitive functioning and brain development are summarized, while the structural related brain changes are excluded as the technical nature of the changes are beyond the scope of this review.

To assess brain function studies have paired imaging techniques, such as functional magnetic resonance imaging (fMRI), with cognitive testing. The results have shown there are abnormalities in brain activity, but these results have varied based on the specific study parameters, the variations within each subject, and the subjects' level of cannabis use. The authors of a review of cannabis

effects on brain structure, function, and cognition note most of the studies conclude there are changes in brain function (Burggren et al., 2019). A review in the American Journal of Medicine (deShazo et al., 2019) summarizes that meta-analyses report regular marijuana users, compared to non-users, have "diminished executive function, attention, learning, memory, and motor skills that persist for varying times after abstinence occurs." Changes in brain morphology (structure) have been observed in the medial temporal and frontal cortex, and the cerebellum. The degree of changes in these portions of the brain may reflect the degree of cannabis use.

Age-related cannabis use

The endocannabinoid system impacts growth, differentiation, positioning, and connectivity of neurons. When exogenous cannabinoids, such as THC, are introduced they may disrupt the endocannabinoid system and thus neural development, especially during adolescence (Sagar and Gruber, 2018). The meta-analysis from Scott and colleagues (2018) identified limited associations between cannabis use and cognitive functioning among adolescents and young adults. The authors conclude that cognitive deficits associated with cannabis use were diminished after three days of abstinence. Additionally, the authors suggest previous studies examining the cognitive deficits associated with cannabis use may overstate the association, in terms of magnitude and persistence of deficits. This was contradicted by the findings of Burggren and colleagues (2019), which reported that findings from cross-sectional studies conclude impairments in attention, verbal and working memory, and psychomotor speed remains in abstinent adolescents for between 28-35 days. Of the studies reviewed by the authors, memory, attention, decision making, and inhibitory control in adolescents found abnormal brain functioning activation patterns. They concluded poorer cognitive performance was associated with cumulative cannabis use and earlier age of onset of use. Jacobus and colleagues (2019) suggested recency, frequency, and age of first cannabis use may predict cognitive and emotional functioning. Sagar and Gruber (2018) agree, as they report adolescent use is potentially more dangerous than use in adulthood, as it is a critical period of neurodevelopment that is vulnerable to the exogenous influence of marijuana. The authors also highlight greater rates of marijuana use in older adults (ages 55-64), which they suggest could be problematic as the metabolism of marijuana in this population could be slower, possibly contributing to greater intoxication or adverse events. A potential mechanism is through interaction with prescription drugs and altered liver function.

Bloomfield and colleagues (2019) identified a single experimental, placebo-controlled study assessing the developmental effects of cannabis in their review of human imaging studies related to the neuropsychopharmacology of cannabis. This study concluded adolescent cannabis users were resistant to some acute effects of cannabis, such as memory impairment and psychotic-like symptoms, while they were vulnerable to lack of satiety and had impaired inhibitory processing. Based on other studies reviewed, the authors report cannabis effects on the adolescent brain could influence emotional and cognitive function. Thus, early and heavy cannabis use during adolescence can predict poor emotional processing and cognition later in life. As summarized by deShazo and colleagues (2019) The Adolescent Brain Cognitive Development (ABCD) Study will help to elucidate the impact of cannabis use during adolescence. The ABCD study is a prospective, longitudinal (10 year) study of 10,000 9-10-year-old children in the US, that will collect data on brain imaging, psychometric and psychosocial assessments, academic performance, genetic testing, and substance use.

Behavioral impacts of cannabis use

Executive functioning: The authors of a review (Sagar and Gruber, 2018) summarized that other review articles generally agreed that marijuana use adversely impacts memory and executive functioning. This was supported by another review article (Burggren et al., 2019), which reported there was substantial evidence that acute use of cannabis adversely impacted executive function. Impaired performance for tasks involving planning, reasoning, interference control, and problem solving were observed in some studies.

General intelligence (IQ): There is not a consensus on the impact of cannabis use on IQ (Sagar and Gruber, 2018). Based on another review, regular cannabis use during adolescence and the transition to adulthood may cause lasting negative effects on cognitive functioning and IQ. However, a number of recent studies reported that there was no evidence that adolescent use or dependence was associated with a decrease in IQ or neurocognitive performance (Burggren et al., 2019).

Attention and Memory: Differences between users and non-users have been observed in attention, as long-term cannabis users can have lasting impairment in memory and attention, with greater impairment with increased use (Burggren et al., 2019). According to Figueiredo and colleagues (2020) chronic cannabis use has the strongest association with impairment in long- and short-term memory. Chronic cannabis use was also associated with increased cognitive impulsivity, impaired cognitive flexibility, and impaired attention. Attention was described as the ability to reject irrelevant information while focusing on relevant input, and to identify unpredictable signals over long periods of time. Bloomfield et al. (2019) supported this, summarizing that disruptions of memory and learning are among the most widely replicated effects of cannabis use. Sagar and Gruber (2018) report there was agreement among review articles that marijuana use negatively impacts memory. Strong evidence was reported for impairment in verbal memory for recreational marijuana users, but it was less clear what role marijuana use plays in associative and visuospatial memory. Burggren and colleagues (2019) agreed, summarizing that verbal learning and memory are sensitive to acute and chronic cannabis use. They also reported sex-related differences, with worse episodic memory associated with use in females compared to males, and worse decision-making performance in males. There may be a dose-dependent relationship as abstinence may improve verbal memory, and increased use showed worse impairments in memory and attention.

Motor impulsivity: A systematic review and meta-analysis (Figueiredo et al., 2020) did not find an association between chronic cannabis use and motor impulsivity.

Processing speed: In cross-sectional studies comparing adolescent cannabis users with non-users, cannabis users had poorer performance on tests of processing speed (Jacobus et al., 2019). Sagar and Gruber (2018) reported that review articles had a consensus that marijuana use negatively impacts processing speed.

Reaction time: In measured reaction time, through testing of inhibitory control (go/no-go or stop-signal tasks), findings were mixed among chronic cannabis users. There was increased reaction time reported among occasional and heavy cannabis users (Burggren et al., 2019).

Risk taking: Mixed findings were reported related to risk taking, as there were reported differences between users and non-users in both laboratory testing results and self-reported questionnaires. Both infrequent and regular cannabis users were reported to increase risk-taking behaviors after THC use, but this was not observed in all studies related to decision-making (Burggren et al., 2019).

Tolerance: The review of pharmacodynamic and behavioral models of cannabis tolerance (Ramaekers et al., 2020) suggested that cannabis users do not have self-control over a wide range of indicators of impairment, which some users think they do when they perceive to have built up a tolerance. Tolerance was defined as users having control over functional impairments caused by cannabis use. Tolerance was assessed to occur among cannabis users whom continuously use high doses, over a long period of time, and was only a temporary state that fluctuated based on use.

Reward processing: Cannabis use is reported to dampen anticipatory reward processing, so chronic use could increase vulnerability to mental health disorders, such as addiction to other substances, gambling, depression, and psychosis (Bloomfield et al., 2019).

Psychosis: Schoeler and colleagues (2017) reported there was a difference in adherence to medication prescribed for psychosis among different types of cannabis users. Those that used high-potency ("skunk-like") forms of cannabis were significantly less likely to adhere to their prescriptions in comparison to never-regular users; sporadic users or those that used "milder" forms of cannabis did not significantly differ in their medication adherence. Sideli and colleagues (2018) described that the combination of lifetime cannabis use and childhood abuse (sexual or physical) increased the odds for psychosis by almost three times, as compared to each individually; when controlling for confounders, however, the association was not statistically significant. Murray and colleagues (2017) concluded that human laboratory studies have demonstrated THC and other cannabinoids can cause temporary positive and negative psychotic symptoms and can mimic the cognitive and neurophysiological changes found in schizophrenia. Additionally, the authors suggested THC seems to modulate salience processing (attention), which they suggest could induce psychotic symptoms or make them worse.

Schizophrenia: A combination of neurocognitive, neurochemical, and structural changes could culminate in clinical schizophrenia from cannabis use in those considered vulnerable to the negative effects of cannabis use. Hallucinations, paranoia, lack of motivation, and cognitive impairment have been associated with acute THC exposure and long-term, heavy cannabis use. Each of these are associated with neuropharmacological effects of cannabis, as it can impact working memory performance, altered threat processing, and generate anxiety. Thus, two possible mechanisms are proposed by the authors: "(1) cannabis is exacerbating the same vulnerabilities that cause idiopathic schizophrenia and (2) cannabis causes additional routes to the phenotype." Additionally, the authors proposed that there could be a distinct subtype of schizophrenia proceeding heavy cannabis use (Bloomfield et al., 2019). It was noted by the authors of a different review that schizophrenia patients with cannabis abuse demonstrated improved emotional memory when compared to schizophrenic patients without cannabis use (Burggren et al., 2019).

Summary and recommendations

Review articles suggest cannabis use impacts brain development and functioning. The severity of impact and length of observed effects vary based upon several factors, including age of onset of use, length of use, frequency of use, type of cannabis used (concentration, ratio of THC to cannabidiol [CBD]), and possibly gender. There was largely agreement among articles that chronic use is associated with changes in mood and cognition (deShazo, 2019). Importantly, cannabis use while the brain is still developing is not advised due to the potential of long-term effects.

Recommendations based on the literature included improving experimental design to study the long-term effects of cannabis use (Burggren et al., 2019). Ramaekers and colleagues (2020) suggest experimental studies should measure the level of THC in the blood of study participants and report the blood THC concentrations to control for the method and frequency of cannabis use within and across studies. The authors also mention many studies have design flaws, specifically with inadequate control matching and small sample sizes. Bloomfield and colleagues (2019) also highlight a number of limitations: study participant populations vary greatly; route of administration, dosage, and definition of usage is not standard; some studies provide participants with cannabis to use, while others directly administer THC; and brain functioning imaging methods are diverse and have undergone significant development. Additionally, history of use, age of onset of use, and abstinence of participant cannabis, as well as use of other substances should be, but are not necessarily consistently, included. The composition of the cannabis products consumed in studies, as well as the THC:CBD ratio should be measured. Lastly, instead of retrospective recall of cannabis use, robust prospective study designs should be implemented.

Cannabis concentration and health

The Δ^9-tetrahydrocannabinol (THC) concentration in cannabis products has increased significantly over the past two decades (Chandra et al., 2019). Since 2017, two reviews and seven original research articles have been published investigating the changing trends in THC concentration and the impact on behavior and health.

THC concentration trends

Laboratory testing of United States Drug Enforcement Agency (DEA) cannabis seizures showed an increase in THC concentration in all cannabis products, from 8.9% in 2008 to 17.1% in 2017 (Chandra et al., 2019). European countries including the Netherlands, the United Kingdom, Italy (Chandra et al., 2019) and France (Dujourdy and Mesacier, 2017), all reported increases in THC concentrations in seized cannabis products. Mean tetrahydrocannabinol: cannabidiol (THC: CBD) ratios in United States DEA seizures also rose from 23 in 2008 to 104 in 2017 (Chandra, et al., 2019). European countries reflected that increase (Dujourdy and Mesacier, 2017). Cannabis flower THC concentration from DEA seizures has increased from 6% in 2008 to 13.6% in 2017, which aligns with the average increase (Chandra et al., 2019).

Liquid cannabis concentrate products increased in THC concentration from 6.7% in 2008 to 55.7% 2017. There was also an increase in the proportion of United States DEA seized liquid cannabis concentrate product from 0.5% in 2008 to 4.7% in 2017 (Chandra et al., 2019). In Denmark, THC concentrations increased in seized solid cannabis concentrate products from 8% in 2000 to 25% in 2017 (Thomsen et al., 2019). In drug seizure data, there are limitations; not all drugs seized were tested, and seized drugs were not a uniform sample of what was available in the illicit market.

One review (Struble et al., 2019) and one study (Caulkins et al., 2018) assessed the THC concentration of cannabis products in the Colorado and Washington State legal markets. In 2017, the Colorado Department of Revenue reported the average THC concentration in concentrated cannabis products was 68.6%. Some Colorado dispensaries reported THC concentrations of 85% or more (Struble et al., 2019). In the Washington state legal market, the average THC concentration increased from 50% in 2014 to 75% in 2016. Also, the number of solid and liquid cannabis concentrate product transactions grew by 100% (Caulkins et al., 2018). Though legal market data captured a more reliable sample of cannabis consumed by the population, it did not include the illegal market.

These studies highlighted the increased rate of cannabis concentrate products in the illicit and legal market and the increased THC concentration of all cannabis products (as shown in the following figures adapted from Chandra et al., 2019).

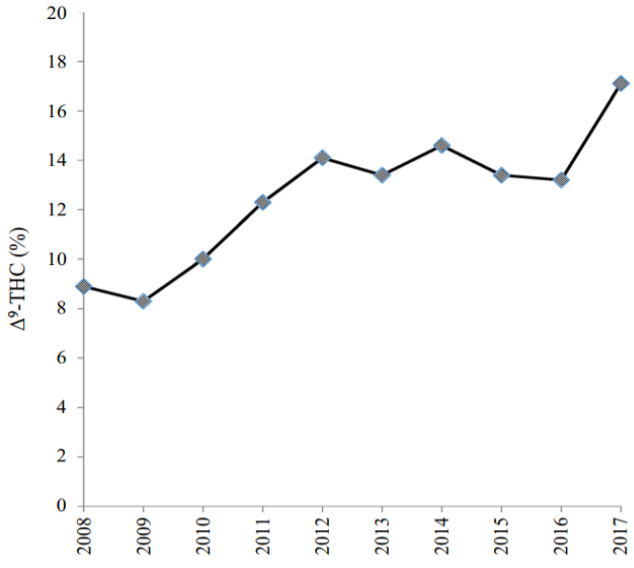


Fig. 2 Mean Δ^9-THC concentration for all samples seized from 2008 to 2017

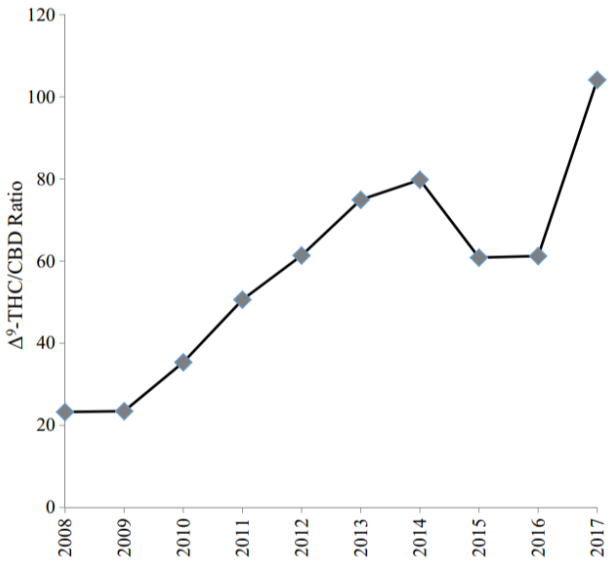


Fig. 4 Ratio of the mean concentration of Δ^9-THC to CBD in across all samples by year

Table 2 Mean and standard deviation (SD) of Δ^9-THC concentration (%) by type of sample and year

Year	All		Cannabis						All cannabis		Hashish		Hash oil	
			Sinsemilla		Marijuana		Ditchweed							
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
2008	8.9	6.7	11.5	6.1	6.0	3.9	0.4	0.3	6.0	3.4	22.8	19.3	6.7	9.3
2009	8.3	6.2	10.8	6.1	5.7	4.2	0.4	0.3	5.6	3.5	21.3	15.3	8.9	9.6
2010	10.0	7.7	12.7	6.1	5.7	4.4	0.5	0.3	6.3	3.6	22.8	16.5	38.3	30.1
2011	12.3	8.9	13.6	6.2	5.6	3.1	0.5	0.2	6.6	3.2	30.0	15.1	37.0	26.2
2012	14.1	11.3	14.5	6.4	6.1	3.7	0.65	0.1	7.1	3.4	31.7	19.1	53.5	25.5
2013	13.4	10.2	13.6	5.9	6.3	3.1	0.5	0.1	6.8	3.0	29.3	16.4	50.0	26.6
2014	14.6	13.5	13.5	6.4	5.8	3.7	0.2	–	6.5	5.1	30.3	23.7	50.8	27.3
2015	13.4	13.2	12.7	6.1	6.8	3.2	0.4	0.3	6.6	3.2	17.6	20.1	56.3	24.9
2016	13.2	10.8	15.0	5.6	7.3	3.4	0.8	0.1	7.7	3.0	15.5	14.3	37.9	26.6
2017	17.1	12.9	17.8	5.1	9.4	4.7	0	0	13.6	4.9	45.9	26.6	55.7	24.7

Cannabis concentrate use patterns

THC concentration in all cannabis products have increased, and use of cannabis concentrate products, which have the highest THC concentration, have increased. Because of this, studies have sought to understand the impact of this increase on cannabis use patterns.

One study showed adolescents who used cannabis concentrate products had higher cannabis use at follow-up points of 6 and 12 months compared to individuals using other forms of cannabis (i.e. blunt, vaping or edible use) (Barrington-Trimis et al., 2020). Another study found a form of liquid cannabis concentrate, butane hash oil, was associated with higher levels of physical dependence than other forms of cannabis consumption, even when considering several confounding variables (Meier, 2017). Both studies had statistically significant findings, but note cannabis concentrate users were the smallest group of cannabis users. The authors recommended targeting prevention towards cannabis concentrate users as a smaller, high risk group (Barrington-Trimis et al., 2020; Meier 2017).

One study examined the United States' national THC concentration trends and their correlation with cannabis treatment trends in Michigan. Results indicated that as the national THC concentration increased in seized cannabis products, the risk of earlier cannabis use disorder (CUD) symptom onset increased. The risk of earlier onset of regular use or onset of daily use did not increase. Though this study showed a correlation between increased THC concentration trends and faster progression to CUD, correlation is not causation. A potential limitation of this study was the lack of use of state specific THC concentration trends (Arterberry et al., 2019).

An additional study (Cavazos-Rehg et al., 2018) examined the use patterns of individuals who use cannabis concentrate. All participants were individuals who used cannabis concentrate, and 27.8% reported using cannabis concentrates at least 10 days in the past month. This study found that 52.1% of participants believed they could perform their everyday activities very well when using cannabis concentrates. Also, 57.7% of study participants reported using cannabis concentrates with alcohol and 22.6% reported using cannabis concentrates with other drugs in the past month. Individuals who reported use of cannabis concentrates along with alcohol or other drugs in the last month had almost twice the odds of reporting side effects which included a sense of altered reality and confusion (23.3%), rapid heartbeat (11.2%), lung pain (9.9%), and severe paranoia (6.9%). This study highlighted the need to understand the effects of using cannabis concentrates with other drugs and target education to cannabis concentrate users about concomitant use.

These studies show that increased use of cannabis products with a high THC concentration, specifically cannabis concentrate products, could increase the negative impacts of cannabis use.

Behavioral and other health effects of cannabis concentrates

As THC concentrations in cannabis products have increased, and use of cannabis concentrate products have increased, studies have sought to understand the impact of this on health. In college students, one study found that a form of liquid cannabis concentrate, butane hash oil, was related to greater academic, occupational, interpersonal, personal hygiene problems, and risky behaviors. Use of butane hash oil has also been linked to increased cannabis tolerance and withdrawal symptoms like confusion, impaired memory, reality distortions, and losing consciousness (Struble et al., 2019).

One case review (Struble et al., 2019) identified three cases of severe psychotic symptoms after using liquid cannabis concentrate, and one case study examined a case of pneumonitis with acute hypoxic respiratory failure associated with liquid cannabis concentrate use. One cross-sectional study (Prince and Conner, 2019) showed individuals who reported mental health symptoms (i.e. mania, anger, anxiety, and depression) also reported higher THC concentrations in their cannabis concentrate products. In the same study, those who reported physical health problems (i.e. respiratory problems, ears, nose, and throat problems, and cardiovascular problems) also reported using concentrated cannabis products with higher THC concentration. In this study, methods of cannabis use were split between cannabis flower and cannabis concentrate. THC concentrations in cannabis flower products showed limited association with negative health outcomes, while THC concentration in cannabis concentrate product were associated with negative health outcomes (Prince and Conner, 2019). This underscores the importance of determining the cannabis product and its THC concentrations when assessing association with health outcomes in future studies.

A multinational case-control study (Di Forti et al., 2019) concluded individuals with daily use of cannabis products with high THC concentrations (>10% THC) had a higher risk of psychosis than individuals who did not use.

Though case series and cross-sectional studies can be used to identify and describe a problem, the case-control study by Forti and colleagues (2019) showed a strong link between cannabis products with high THC concentration and psychosis.

The health impacts of high THC concentration cannabis products were manifested in the accidental poisonings of children. A review (Claudet et al., 2017) of pediatric cannabis poisonings identified an increase related to solid cannabis concentrate products in the most recent year of the study. All of those children were admitted to the pediatric intensive care unit. This corresponds to the increase in potency in cannabis concentrates seen in France (Dujourdy and Mesacier, 2017).

Conclusion

THC concentration has increased across all cannabis products in the past decades, but most markedly in cannabis concentrate products. At the same time, there has been an observed increase in use of cannabis concentrate products. There were few new studies investigating the impact of the cannabis concentration increase on health, and more research is called for to understand the public health implications.

Impact of cannabis use on driving

From the rapid review, there are several studies and literature reviews that address the aspects of driving under the influence of cannabis. Of the studies reviewed, four assessed the impacts of cannabis on driving performance using a driving simulator. The results from these studies suggested a general consensus that driving under the influence of cannabis, especially acutely after cannabis consumption, leads to a reduction in driving performance and an increase in overall crash risk.

Tank and colleagues (2019) investigated the effects cannabis had on traffic safety by analyzing multiple health and driving variables following the completion of a driving simulation under the influence of cannabis. The findings suggested that in the acute phase of post-cannabis consumption, driving mistakes such as lane departure, accidents due to unforeseeable events, and running yellow/red lights were more common. Ogourtsova and colleagues (2018) examined the impact of cannabis on driving performance, useful field of view (UFOV; the visual field in which information can be acquired and processed), and self-reported perceptions on one's ability to drive. The participants were block-randomized into 4 test sessions: without cannabis and at 1, 3 and 5 hours after cannabis use. The authors concluded, among young recreational cannabis users, using cannabis did not impact simple and learned tasks. However, it did result in significant impairments on complex and novel driving-related tasks, and perceived driving ability and safety for up to five hours after use. Researchers noted that the study results cannot be extrapolated to chronic and/or daily cannabis users.

A meta-analysis conducted by Hostiuc and colleagues (2018) reviewed over 24 articles associated with driving under the influence of cannabis (DUIC) and its association with unfavorable traffic events (UFE). The authors noted that the way DUIC was determined varied amongst studies, which could have impacted the way unfavorable traffic events were assessed. Examples of variation in determining DUIC included methodological differences, such as using self-reported cannabis use data from test subjects, determining DUIC through THC blood level tests, and the differing definitions of what constituted high-risk cannabis use. The authors concluded that drivers interpreted to be DUIC should have their cannabis use confirmed using clear objective data, such as a clinical assessment or blood analysis before establishing their fitness to drive.

Other studies and analyses have also shown associations between cannabis use and traffic fatalities in states where cannabis is legal. In particular, Steinemann et al. (2018) analyzed Hawaii's Fatality Analysis Reporting System (FARS) data from before (1993-2000) and after (2001-2015) cannabis legalization and found that THC positive blood samples among fatally injured drivers was roughly three times higher after the legalization of cannabis compared to before legalization. This data is supported by Hawaii's highest-level trauma center data, which showed vehicle crash patients that tested positive for THC increased from 11% to 20% following legalization. These patients were also more likely to not be wearing a seatbelt or helmet.

Lane and Hall (2019) reviewed monthly traffic fatality counts through the Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research (WONDER) web application in three states that had recently legalized cannabis (Colorado, Washington, Oregon), as well as their neighboring states. They found a temporary increase in traffic fatalities in legalizing states, with a varied "spill-over" effect in neighboring states. It should be noted that the traffic fatality data was not specific to cannabis or other substance use.

Martin and colleagues (2017) found that out of 2,870 fatal accidents in Metropolitan France in 2011, 4.8% of the responsible drivers had THC alone in their system, and 6% had both THC and alcohol in their system. The crude odds ratio (OR) associated with being responsible for a fatal vehicle accident under the influence of cannabis was 3.45 times greater compared to drivers with no substance use. The cumulative risks of both alcohol and cannabis together will likely continue to contribute to motor vehicle accidents and fatalities.

It should be noted that the reviewed studies are not without their limitations. Specifically, while driving simulators are useful in predicting actual driving behavior, they are not identical to driving an actual vehicle. Other limitations include the potency of the research grade cannabis used in each study. This type of cannabis may be stronger or weaker than the cannabis that each test subject may use recreationally. The small sample sizes in both driving simulator studies should also be mentioned. In regard to the studies and analysis of cannabis's impact on traffic fatalities there are also limitations. In most studies, fatally injured drivers that tested positive for THC had also consumed alcohol, which limits the responsibility attributable to cannabis. The lag time between crash and blood sample collection also has an impact on factors such as odd ratio (OR) estimates and the attribution of crash responsibility. A more specific limitation found in the study conducted by Lane and Hall (2019) was that the traffic fatality data they reviewed was not specific to any substance use.

Recommendations for future studies that analyze cannabis's effect on driving performance variables are to have a suitable sample size of participants. In addition, studies should categorize participant's recreational cannabis use as either: non-cannabis users, moderate cannabis users, or high cannabis users. Researchers should also ensure the potency, strain and dosage of research grade cannabis is standard across the study and any subsequent studies. Another recommendation is to continue conducting test sessions at standard timeframes following cannabis use (i.e. 1,3, 5 hours post cannabis use). For the analysis of motor vehicle fatalities and crashes, and their association with cannabis use, cases should be categorized based on the type of specific substances found in blood, particularly those with only THC found in blood samples, only alcohol found in blood samples and those with THC and alcohol found in blood samples. This could allow researchers to draw more accurate conclusions on THC's influence on motor vehicle crashes and

fatalities.

Harm reduction and marijuana use

In the context of marijuana use, harm reduction does not have a clear definition. In the 2016 document, "Health Impact Assessment: Marijuana Regulation in Vermont" and its 2017 literature review update, increases in THC concentration over time, high frequency of use, and early initiation of use are pointed to as areas of concern with respect to negative health outcomes. Thus, a possible/plausible conclusion is that low-THC marijuana, decreased frequency of use, and later onset of use are viable options for harm reduction. Because this topic was not previously explored in the 2016 health impact assessment or its literature review update, this summary of the literature includes publications from 2016 to present.

Protective behavioral strategies for marijuana use

Pedersen et al. (2016) developed a list of "protective strategies that marijuana users employ before, during, after, or instead of using marijuana to limit heavy use and minimize potential negative consequences." This was done through an iterative process that involved the authors generating lists of protective strategies based on the literature, discussions with colleagues in the field, and college marijuana users. The resulting list of 50 strategies was narrowed down to 39 strategies using a principal components analysis. Among past 6-month users (n=47), the 39 strategies were found to be significantly negatively correlated with marijuana use consequences and cannabis use disorder symptoms. Similarly, among past-month users (n=163), the 39 strategies were significantly negatively correlated with days used, times used per day, marijuana use consequences, and cannabis use disorder symptoms.

Pedersen et al. (2017) further narrowed the list of 39 marijuana protective behavioral strategies to a 36-item list and a 17-item subset designed to be "free of bias in terms of gender (men versus women), race (White versus non-White), ethnicity (Hispanic versus non-Hispanic), and recreational marijuana use legal status" in the respondent's state of residence. This was also done using a factor analysis approach. Both the 36- and 17-item lists were significantly negatively correlated with days used, days used to the point of being high, days passed out or sick due to marijuana use, and marijuana consequences. Both lists were significantly positively correlated with age at first use of marijuana. The 36-item list of marijuana protective behavioral strategies is presented (see following figure adapted from Pedersen et al., 2017).

36-item version of the Protective Behavioral Strategies for Marijuana Scale (PBSM-36)

1	Use marijuana only among trusted peers
2	Avoid use while spending time with family
3	Avoid using marijuana before work or school
4	Avoid using marijuana to cope with emotions such as sadness or depression
5	Do not keep marijuana in the car, whether as a driver or passenger
6	Avoid bringing marijuana into events or venues where you are likely to be searched
7	Limit use to weekends

8	Avoid driving a car after using
9	Only purchase marijuana from a trusted source
10	Avoid using marijuana habitually (that is, every day or multiple times a week)
11	Avoid using marijuana early in the day
12	Keep track of your costs to get an accurate picture of how much you spend on marijuana
13	Avoid using marijuana for several days in advance of a big test, interview, performance, or other engagement for which you need to be crisp and are being evaluated
14	Use a little and then wait to see how you feel before using more
15	Avoid buying marijuana
16	Avoid mixing marijuana with other drugs
17	Only use at night (that is, not during the day)
18	Stop using marijuana if you become anxious or paranoid
19	Avoid using marijuana in public places
20	Take periodic breaks if it feels like you are using marijuana too frequently
21	Buy less marijuana at a time so you smoke less
22	Avoid situations that you anticipate being pressured to use marijuana
23	Only use when you know you have nothing important to do for the rest of the day/night
24	Have a set amount of "times" you take a hit (e.g., passing on a shared joint if you have already hit that limit)
25	Avoid using marijuana out of boredom
26	Avoid methods of using marijuana that can make you more intoxicated than you would like (e.g., using large bongs, volcano, 'edibles,' etc.)
27	Pass on shared joints, bongs, etc. if already feeling high
28	Only use one time during a day/night
29	Avoid using marijuana in large gatherings or crowds
30	Limit the amount of marijuana you smoke in one sitting
31	If attending a party or going out to a social event (e.g., bar), decide in advance whether
32	Avoid using when feeling anxious (e.g., using to calm you down or stop worrying)
33	Avoid using marijuana in concentrated forms (e.g., hashish, hashish/honey oil, kief, marijuana butter/oil, etc.) to avoid getting too high
34	To decrease tolerance, take a break for a week or two, or take longer breaks than usual between use
35	Use enough only to achieve a slight buzz or to avoid getting "too high"
36	Avoid using marijuana before engaging in physical activity (i.e., exercise, hiking)

Much of the literature discussing marijuana protective behavioral strategies is written by the Marijuana Outcomes Study Team (MOST) and the Protective Strategies Study Team (PSST). Both are research collectives composed of individuals from multiple institutions across the US.

Project MOST: Pearson et al. (2017) surveyed 8,141 university students from psychology department participant pools across 11 US college campuses. They found that use of marijuana protective behavioral strategies was negatively correlated with marijuana use. These results were reproduced by Pedersen et al. (2017), Bravo et al. (2017a), Bravo et al. (2017), Wilson et al. (2018), Parnes et al. (2018), and Neugebauer et al. (2019). All publications found that use of marijuana protective behavioral strategies significantly mediated marijuana use frequency and negative consequences experienced by individuals who used.

Project PSST: Bravo et al. (2018) surveyed 7,307 university students from psychology department participant pools across 10 US college campuses. Using the previously collected data, Bravo et al. (2019) found that use of protective behavioral strategies was significantly negatively associated with marijuana use quantity and marijuana-related consequences. Similarly, Jordan et al. (2019) found that use of protective behavioral strategies was significantly negatively associated with marijuana use frequency/quantity, cannabis use disorder symptoms, and marijuana-related problems.

Other research: Pedersen et al. (2018) studied the use of protective behavioral strategies among young adult veteran marijuana users and found a significant negative relationship between the use of such strategies and marijuana use frequency and consequences.

Other information related to harm reduction

Due to the lack of a definition for harm reduction in the context of marijuana use, harm reduction research is limited and unfocused, apart from research related to protective behavioral strategies. Much of the information about harm reduction is written in the form of commentary papers and conclusions. Thus, the information presented below requires more research.

Freeman and Lorenzetti (2019) proposed using a “Standard Cannabis Unit” of 5mg THC to reduce potential harms associated with marijuana use. This measure would be used “across all cannabis products and methods of administration.” In a commentary, Chester et al. (2020) supported the idea of the standard 5mg dose and further emphasized the potential for CBD to reduce negative effects related to THC consumption, although research about concurrent CBD use is conflicting at present.

A study of Uruguayan cannabis social clubs (Pardal et al., 2019) found that social clubs, which operate similarly to dispensaries in the US, do not regularly collaborate with health professionals or harm reduction organizations and found that in one case, staff had directed customers toward vaping as a healthier alternative to smoking marijuana.

The issues of formal guidance and the role of dispensary staff were further reflected in a 2020 commentary about the need for clinician engagement with patients with regard to marijuana use (Calcaterra et al., 2020). The authors addressed dispensary workers providing medical advice to customers in lieu of formal dosing or safety recommendations. This commentary specifically referred to the medical marijuana setting, but it implied a broader need for guidance surrounding safe use.

Conclusions

From a public health messaging standpoint, the negative association between protective behavioral strategies and negative self-reported outcomes related to marijuana use is promising. However, there is a paucity of research exploring the effects of specific protective behavioral strategies. In other words, it is not known which specific strategies are most strongly associated with frequency of use and negative health outcomes. Additionally, negative health outcomes are typically described using composite scores, making it impossible to determine which negative health outcomes are associated with which protective behavioral strategies based on the current literature.

Further, study data have almost exclusively been gathered from samples of college students and young adults, mostly in psychology department research pools. Young adults (18 to 25 years old) are statistically more likely to use marijuana than other age groups. While this may warrant a focus on this age group within the literature, results cannot be generalized to the rest of the adult population.

Research on the topic of harm reduction apart from protective behavioral strategies is limited. Based on the current research, there is no evidence to determine whether a standardized dosage of THC will reduce harms associated with use, and the idea of formal guidance related to marijuana use is somewhat nebulous which would make its impact difficult to measure. Based on the current literature, further exploration into the efficacy of specific protective strategies and how they mitigate specific risk factors associated with marijuana use is necessary.

Final conclusions

Based upon this rapid review of the research literature regarding cannabis or marijuana and health, there continue to be significant gaps in the knowledge. However, there does seem to be loose agreement on a number of health topics: cannabis use should be avoided during brain development (prenatally through adolescence) and use in moderation (in terms of frequency and THC concentration) is associated with fewer negative health outcomes. Additionally, the findings suggest acute cannabis use may have a negative impact on accurately processing moderate to complex tasks. Thus, it is not recommended individuals operate motor vehicles, heavy machinery or other related equipment, immediately following cannabis use to reduce the chances and cases of injury or death.

While methods of cannabis or marijuana consumption continue to evolve, and the products which are correspondingly used with them, the initial conclusions about cannabis use may change. As mentioned in the THC concentration section, the average THC concentration of flower and concentrate products has been significantly increasing. Thus, research conclusions from ten years ago may be less applicable to today's cannabis use and related health impacts. Similarly, different modes of use, such as dabbing and vaping, may impact which cannabinoids and other chemicals are delivered to the body and how the body metabolizes them. As research in the United States is limited to use of federally supplied cannabis, the cannabis products used in research do not reflect what is available in the consumer legal or illicit market. Consequently, it is difficult to make evidence-based recommendations on cannabis use when the common types of products and modes of consumption have not been extensively studied.

References

Ad, W., Ks, M., Aj, B., Bt, C., & Mr, P. (2018). Making Decisions with Trees: Examining Marijuana Outcomes among College Students using Recursive Partitioning. *Clin Psychol Sci, 6*(5). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31106039

Alshaarawy, O., & Anthony, J. C. (2019). Cannabis use among women of reproductive age in the United States: 2002-2017. *Addict Behav, 99*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31421581

Arterberry, B. J., Treloar Padovano, H., Foster, K. T., Zucker, R. A., & Hicks, B. M. (2019). Higher average potency across the United States is associated with progression to first cannabis use disorder symptom. *Drug Alcohol Depend, 195*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30573162

Atapattu, S. N., & Johnson, K. R. D. (2019). Pesticide analysis in cannabis products. *J Chromatogr A*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31679712

Barrington-Trimis, J. L., Cho, J., Ewusi-Boisvert, E., Hasin, D., Unger, J. B., Miech, R. A., & Leventhal, A. M. (2020). Risk of Persistence and Progression of Use of 5 Cannabis Products After Experimentation Among Adolescents. *JAMA Netw Open, 3*(1). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31977062

Bloomfield, M., Hindocha, C., Green, S. F., Wall, M. B., Lees, R., Petrilli, K., Costello, H., Ogunbiyi, M. O., Bossong, M. G., & Freeman, T. P. (2019). The neuropsychopharmacology of cannabis: A review of human imaging studies. *Pharmacol Ther*, *195*, 132–161. Retrieved from https://doi.org/10.1016/j.pharmthera.2018.10.006

Bravo, A. J., Anthenien, A. M., Prince, M. A., & Pearson, M. R. (2017a). Marijuana protective behavioral strategies as a moderator of the effects of risk/protective factors on marijuana-related outcomes. *Addict Behav, 69*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/28110137

Bravo, A. J., Prince, M. A., & Pearson, M. R. (2017). Can I Use Marijuana Safely? An Examination of Distal Antecedents, Marijuana Protective Behavioral Strategies, and Marijuana Outcomes. *J Stud Alcohol Drugs, 78*(2). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/28317500

Bravo, A. J., Villarosa-Hurlocker, M. C., & Pearson, M. R. (2018). College student mental health: An evaluation of the DSM-5 self-rated Level 1 cross-cutting symptom measure. *Psychol Assess, 30*(10). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30070557

Bravo, A. J., Weinstein, A. P., & Pearson, M. R. (2019). The Relationship Between Risk Factors and Alcohol and Marijuana Use Outcomes Among Concurrent Users: A Comprehensive Examination of Protective Behavioral Strategies. *J Stud Alcohol Drugs, 80*(1). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30807281

Burggren, A. C., Shirazi, A., Ginder, N., & London, E. D. (2019). Cannabis effects on brain structure, function, and cognition: considerations for medical uses of cannabis and its derivatives. *Am J Drug Alcohol Abuse, 45*(6). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31365275

Calcaterra, S. L., Cunningham, C. O., & Hopfer, C. J. (2020). The Void in Clinician Counseling of Cannabis Use. *J Gen Intern Med*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31898125

Carlier, J., Huestis, M. A., Zaami, S., Pichini, S., & Busardò, F. P. (2019). Monitoring the effects of perinatal cannabis and synthetic cannabinoid exposure. *Ther Drug Monit*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31268967

Caulkins, J. P., Bao, Y., Davenport, S., Fahli, I., Guo, Y., Kinnard, K., . . . Kilmer, B. (2018). Big data on a big new market: Insights from Washington State's legal cannabis market. *Int J Drug Policy, 57*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29709847

Cavazos-Rehg, P. A., Krauss, M. J., Sowles, S. J., Floyd, G. M., Cahn, E. S., Chaitan, V. L., & Ponton, M. (2018). Leveraging user perspectives for insight into cannabis concentrates. *Am J Drug Alcohol Abuse, 44*(6). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29513625

Cecconi, S., Rapino, C., Di Nisio, V., Rossi, G., & Maccarrone, M. (2019). The (endo)cannabinoid signaling in female reproduction: What are the latest advances? *Prog Lipid Res, 77*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31862482

Chandra, S., Radwan, M. M., Majumdar, C. G., Church, J. C., Freeman, T. P., & ElSohly, M. A. (2019). Correction to: New trends in cannabis potency in USA and Europe during the last decade (2008-2017). *Eur Arch Psychiatry Clin Neurosci, 269*(8). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31123822

Chester, L., Chesney, E., Oliver, D., Wilson, J., & Englund, A. (2020). How experimental cannabinoid studies will inform the standardized THC unit. *Addiction*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/32022348

Claudet, I., Le Breton, M., Bréhin, C., & Franchitto, N. (2017). A 10-year review of cannabis exposure in children under 3-years of age: do we need a more global approach? *Eur J Pediatr, 176*(4). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/28210835

Cook, J. L., Green, C. R., de la Ronde, S., Dell, C. A., Graves, L., Ordean, A., . . . Wong, S. (2017). Epidemiology and Effects of Substance Use in Pregnancy. *J Obstet Gynaecol Can, 39*(10). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/28935056

Cooper, Z. D., & Craft, R. M. (2018). Sex-Dependent Effects of Cannabis and Cannabinoids: A Translational Perspective. *Neuropsychopharmacology, 43*(1). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/28811670

Cousijn, J., Núñez, A. E., & Filbey, F. M. (2018). Time to acknowledge the mixed effects of cannabis on health: a summary and critical review of the NASEM 2017 report on the health effects of cannabis and cannabinoids. *Addiction, 113*(5). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29271031

Cox, E. J., Maharao, N., Patilea-Vrana, G., Unadkat, J. D., Rettie, A. E., McCune, J. S., & Paine, M. F. (2019). A marijuana-drug interaction primer: Precipitants, pharmacology, and pharmacokinetics. *Pharmacol Ther, 201*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31071346

DeFilippis, E. M., Bajaj, N. S., Singh, A., Malloy, R., Givertz, M. M., Blankstein, R., . . . Vaduganathan, M. (2020). Marijuana Use in Patients With Cardiovascular Disease: JACC Review Topic of the Week. *J Am Coll Cardiol, 75*(3). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31976871

deShazo, R. D., Parker, S. B., Williams, D., Ingram, J. B., Elsohly, M., Rodenmeyer, K., & McCullouch, K. (2019). Marijuana's Effects on Brain Structure and Function: What Do We Know and What Should We Do? A Brief Review and Commentary. *Am J Med*, *132*(3), 281–285. Retrieved from https://doi.org/10.1016/j.amjmed.2018.09.006

Di Forti, M., Quattrone, D., Freeman, T. P., Tripoli, G., Gayer-Anderson, C., Quigley, H., . . . Murray, R. M. (2019). The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *Lancet Psychiatry, 6*(5). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30902669

Dujourdy, L., & Besacier, F. (2017). A study of cannabis potency in France over a 25 years period (1992-2016). *Forensic Sci Int, 272*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/28122324

El Marroun, H., Brown, Q. L., Lund, I. O., Coleman-Cowger, V. H., Loree, A. M., Chawla, D., & Washio, Y. (2018). An epidemiological, developmental and clinical overview of cannabis use during pregnancy. *Prev Med, 116*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30171964

Esmaeelzadeh, S., Moraros, J., Thorpe, L., & Bird, Y. (2018). Examining the Association and Directionality between Mental Health Disorders and Substance Use among Adolescents and Young Adults in the U.S. and Canada-A Systematic Review and Meta-Analysis. *J Clin Med, 7*(12). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30551577

Figueiredo, P. R., Tolomeo, S., Steele, J. D., & Baldacchino, A. (2020). Neurocognitive consequences of chronic cannabis use: a systematic review and meta-analysis. *Neurosci Biobehav Rev, 108*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31715191

Franks, A. L., Berry, K. J., & DeFranco, D. B. (2019). Prenatal drug exposure and neurodevelopmental programming of glucocorticoid signalling. *J Neuroendocrinol*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31469457

Freeman, T. P., & Lorenzetti, V. (2019). 'Standard THC units': a proposal to standardize dose across all cannabis products and methods of administration. *Addiction*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31606008

French, C. E., Coope, C. M., McGuinness, L. A., Beck, C. R., Newitt, S., Ahyow, L., . . . Oliver, I. (2019). Cannabis use and the risk of tuberculosis: a systematic review. *BMC Public Health, 19*(1). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31351454

Ghasemiesfe, M., Ravi, D., Vali, M., Korenstein, D., Arjomandi, M., Frank, J., . . . Keyhani, S. (2018). Marijuana Use, Respiratory Symptoms, and Pulmonary Function: A Systematic Review and Meta-analysis. *Ann Intern Med, 169*(2). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29971337

Ghosh, M., & Naderi, S. (2019). Cannabis and Cardiovascular Disease. *Curr Atheroscler Rep, 21*(6). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30980200

Gobbi, G., Atkin, T., Zytynski, T., Wang, S., Askari, S., Boruff, J., . . . Mayo, N. (2019). Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood: A Systematic Review and Meta-analysis. *JAMA Psychiatry, 76*(4). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30758486

Guille, C., & Aujla, R. (2019). Developmental Consequences of Prenatal Substance Use in Children and Adolescents. *J Child Adolesc Psychopharmacol*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31038354

Hamilton, I., & Monaghan, M. (2019). Cannabis and Psychosis: Are We any Closer to Understanding the Relationship? *Curr Psychiatry Rep, 21*(7). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31161275

Hasin, D. S. (2018). US Epidemiology of Cannabis Use and Associated Problems. *Neuropsychopharmacology, 43*(1). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/28853439

Ho, C., Martinusen, D., & Lo, C. (2019). A Review of Cannabis in Chronic Kidney Disease Symptom Management. *Can J Kidney Health Dis, 6*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30828459

Hosseini, S., & Oremus, M. (2019). The Effect of Age of Initiation of Cannabis Use on Psychosis, Depression, and Anxiety among Youth under 25 Years. *Can J Psychiatry, 64*(5). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30373388

Hostiuc, S., Moldoveanu, A., Negoi, I., & Drima, E. (2018). The Association of Unfavorable Traffic Events and Cannabis Usage: A Meta-Analysis. *Front Pharmacol, 9*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29487531

Jacobus, J., Courtney, K. E., Hodgdon, E. A., & Baca, R. (2019). Cannabis and the developing brain: What does the evidence say? *Birth Defects Res, 111*(17). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31385460

Jordan, H. R., Madson, M. B., Bravo, A. J., & Pearson, M. R. (2019). Post-traumatic stress and marijuana outcomes: The mediating role of marijuana protective behavioral strategies. *Subst Abus*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31361581

Kafil, T. S., Nguyen, T. M., MacDonald, J. K., & Chande, N. (2018). Cannabis for the treatment of ulcerative colitis. *Cochrane Database Syst Rev, 11*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30406638

Kansagara, D., Becker, W. C., Ayers, C., & Tetrault, J. M. (2019). Priming primary care providers to engage in evidence-based discussions about cannabis with patients. *Addict Sci Clin Pract, 14*(1). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31787111

Kharbanda, E. O., Vazquez-Benitez, G., Kunin-Batson, A., Nordin, J. D., Olsen, A., & Romitti, P. A. (2020). Birth and early developmental screening outcomes associated with cannabis exposure during pregnancy. *J Perinatol*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31911642

Kuhathasan, N., Dufort, A., MacKillop, J., Gottschalk, R., Minuzzi, L., & Frey, B. N. (2019). The use of cannabinoids for sleep: A critical review on clinical trials. *Exp Clin Psychopharmacol, 27*(4). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31120284

Lane, T. J., & Hall, W. (2019). Traffic fatalities within US states that have legalized recreational cannabis sales and their neighbours. *Addiction, 114*(5). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30719794

Liu, C., Qi, X., Yang, D., Neely, A., & Zhou, Z. (2019). The effects of cannabis use on oral health. *Oral Dis*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31793130

Martin, J. L., Gadegbeku, B., Wu, D., Viallon, V., & Laumon, B. (2017). Cannabis, alcohol and fatal road accidents. *PLoS One, 12*(11). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29117206

Meehan-Atrash, J., Korzun, T., & Ziegler, A. (2019). Cannabis Inhalation and Voice Disorders: A Systematic Review. *JAMA Otolaryngol Head Neck Surg*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31393535

Meier, M. H. (2017). Associations between butane hash oil use and cannabis-related problems. *Drug Alcohol Depend, 179*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/28750253

Memedovich, K. A., Dowsett, L. E., Spackman, E., Noseworthy, T., & Clement, F. The adverse health effects and harms related to marijuana use: an overview review. *CMAJ Open, 6*(3). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30115639

Murray, R. M., Englund, A., Abi-Dargham, A., Lewis, D. A., Di Forti, M., Davies, C., Sherif, M., McGuire, P., & D'Souza, D. C. (2017). Cannabis-associated psychosis: Neural substrate and clinical impact. *Neuropharmacology*, *124*, 89–104. Retrieved from https://doi.org/10.1016/j.neuropharm.2017.06.018

Neugebauer, R. T., Parnes, J. E., Prince, M. A., & Conner, B. T. (2019). Protective Behavioral Strategies Mediate the Relation Between Sensation Seeking and Marijuana-Related Consequences. *Subst Use Misuse, 54*(6). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30648462

Nguyen, A. X., & Wu, A. Y. (2019). Association between cannabis and the eyelids: A comprehensive review. *Clin Exp Ophthalmol*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31747112

Ogourtsova, T., Kalaba, M., Gelinas, I., Korner-Bitensky, N., & Ware, M. A. Cannabis use and driving-related performance in young recreational users: a within-subject randomized clinical trial. *CMAJ Open, 6*(4). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30323055

Pancer, J., & Dasgupta, K. (2019). Effects of Cannabis Use in Youth and Young Adults With Type 1 Diabetes: The Highs, the Lows, the Don't Knows. *Can J Diabetes*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31401053

Pardal, M., Queirolo, R., Alvarez, E., & Repetto, L. (2019). Uruguayan Cannabis Social Clubs: From activism to dispensaries? *Int J Drug Policy, 73*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31336294

Parnes, J. E., Prince, M. A., & Conner, B. T. (2018). A mediated multigroup model examining marijuana use consequences by sexual orientation in us college students. *Addict Behav, 87*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29966964

Pearson, M. R., Liese, B. S., & Dvorak, R. D. (2017). College student marijuana involvement: Perceptions, use, and consequences across 11 college campuses. *Addict Behav, 66*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/27894029

Pedersen, E. R., Huang, W., Dvorak, R. D., Prince, M. A., & Hummer, J. F. (2017). The Protective Behavioral Strategies for Marijuana Scale: Further examination using item response theory. *Psychol Addict Behav, 31*(5). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/28703616

Pedersen, E. R., Hummer, J. F., Rinker, D. V., Traylor, Z. K., & Neighbors, C. (2016). Measuring Protective Behavioral Strategies for Marijuana Use Among Young Adults. *J Stud Alcohol Drugs, 77*(3). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/27172576

Pedersen, E. R., Villarosa-Hurlocker, M. C., & Prince, M. A. (2018). Use of Protective Behavioral Strategies among Young Adult Veteran Marijuana Users. *Cannabis, 1*(1). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29757318

Pinto, J. V., Medeiros, L. S., Santana da Rosa, G., Santana de Oliveira, C. E., Crippa, J. A. S., Passos, I. C., & Kauer-Sant'Anna, M. (2019). The prevalence and clinical correlates of cannabis use and cannabis use disorder among patients with bipolar disorder: A systematic review with meta-analysis and meta-regression. *Neurosci Biobehav Rev, 101*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30974123

Pizzol, D., Demurtas, J., Stubbs, B., Soysal, P., Mason, C., Isik, A. T., . . . Veronese, N. Relationship Between Cannabis Use and Erectile Dysfunction: A Systematic Review and Meta-Analysis. *Am J Mens Health, 13*(6). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31795801

Pratt, M., Stevens, A., Thuku, M., Butler, C., Skidmore, B., Wieland, L. S., . . . Hutton, B. (2019). Benefits and harms of medical cannabis: a scoping review of systematic reviews. *Syst Rev, 8*(1). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31823819

Prince, M. A., & Conner, B. T. (2019). Examining links between cannabis potency and mental and physical health outcomes. *Behav Res Ther, 115*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30497655

Qato, D. M., Zhang, C., Gandhi, A. B., Simoni-Wastila, L., & Coleman-Cowger, V. H. (2019). Co-use of alcohol, tobacco, and licit and illicit controlled substances among pregnant and non-pregnant

women in the United States: Findings from 2006 to 2014 National Survey on Drug Use and Health (NSDUH) data. *Drug Alcohol Depend, 206*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31760250

Ramaekers, J. G., Mason, N. L., & Theunissen, E. L. (2020). Blunted highs: Pharmacodynamic and behavioral models of cannabis tolerance. *Eur neuropsychopharmacol*, *S0924-977X(20)30022-5*. Retrieved from https://doi.org/10.1016/j.euroneuro.2020.01.006

Rajanahally, S., Raheem, O., Rogers, M., Brisbane, W., Ostrowski, K., Lendvay, T., & Walsh, T. (2019). The relationship between cannabis and male infertility, sexual health, and neoplasm: a systematic review. *Andrology, 7*(2). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30767424

Ravi, D., Ghasemiesfe, M., Korenstein, D., Cascino, T., & Keyhani, S. (2018). Associations Between Marijuana Use and Cardiovascular Risk Factors and Outcomes: A Systematic Review. *Ann Intern Med*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29357394

Rein, J. L. (2020). The nephrologist's guide to cannabis and cannabinoids. *Curr Opin Nephrol Hypertens*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31972598

Rodriguez, C. E., Sheeder, J., Allshouse, A. A., Scott, S., Wymore, E., Hopfer, C., . . . Metz, T. D. (2019). Marijuana use in young mothers and adverse pregnancy outcomes: a retrospective cohort study. *BJOG, 126*(12). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31334907

Rømer Thomsen, K., Lindholst, C., Thylstrup, B., Kvamme, S., Reitzel, L. A., Worm-Leonhard, M., . . . Hesse, M. (2019). Changes in the composition of cannabis from 2000-2017 in Denmark: Analysis of confiscated samples of cannabis resin. *Exp Clin Psychopharmacol, 27*(4). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31219274

Ryan, S. A., Ammerman, S. D., & O'Connor, M. E. (2018). Marijuana Use During Pregnancy and Breastfeeding: Implications for Neonatal and Childhood Outcomes. *Pediatrics, 142*(3). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30150209

Sagar, K. A., & Gruber, S. A. (2018). Marijuana matters: reviewing the impact of marijuana on cognition, brain structure and function, & exploring policy implications and barriers to research. *Int Rev Psychiatry, 30*(3). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29966459

Sarris, J., Sinclair, J., Karamacoska, D., Davidson, M., & Firth, J. (2020). Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review. *BMC Psychiatry, 20*(1). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31948424

Scheyer, A. F., Melis, M., Trezza, V., & Manzoni, O. J. J. (2019). Consequences of Perinatal Cannabis Exposure. *Trends Neurosci, 42*(12). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31604585

Schoeler, T., Petros, N., Di Forti, M., Klamerus, E., Foglia, E., Murray, R., & Bhattacharyya, S. (2017). Effect of continued cannabis use on medication adherence in the first two years following onset of psychosis. *Psychiatry Res*, *255*, 36–41. https://doi.org/10.1016/j.psychres.2017.05.009

Sharapova, S. R., Phillips, E., Sirocco, K., Kaminski, J. W., Leeb, R. T., & Rolle, I. (2018). Effects of prenatal marijuana exposure on neuropsychological outcomes in children aged 1-11 years: A systematic review. *Paediatr Perinat Epidemiol, 32*(6). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30335203

Sideli, L., Fisher, H. L., Murray, R. M., Sallis, H., Russo, M., Stilo, S. A., Paparelli, A., Wiffen, B., O'Connor, J. A., Pintore, S., Ferraro, L., La Cascia, C., La Barbera, D., Morgan, C., & Di Forti, M. (2018). Interaction between cannabis consumption and childhood abuse in psychotic disorders:

preliminary findings on the role of different patterns of cannabis use. *Early intervention in psychiatry*, *12*(2), 135–142. Retrieved from https://doi.org/10.1111/eip.12285

Singh, S., Filion, K. B., Abenhaim, H. A., & Eisenberg, M. J. (2020). Prevalence and outcomes of prenatal recreational cannabis use in high-income countries: a scoping review. *BJOG, 127*(1). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31529594

Skelton, K. R., Hecht, A. A., & Benjamin-Neelon, S. E. (2020). Recreational Cannabis Legalization in the US and Maternal Use during the Preconception, Prenatal, and Postpartum Periods. *Int J Environ Res Public Health, 17*(3). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/32024173

Stein, Y., Hwang, S., Liu, C. L., Diop, H., & Wymore, E. (2019). The Association of Concomitant Maternal Marijuana Use on Health Outcomes for Opioid Exposed Newborns in Massachusetts, 2003-2009. *J Pediatr*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31843217

Steinemann, S., Galanis, D., Nguyen, T., & Biffl, W. (2018). Motor vehicle crash fatalaties and undercompensated care associated with legalization of marijuana. *J Trauma Acute Care Surg, 85*(3). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/29787529

Struble, C. A., Ellis, J. D., & Lundahl, L. H. (2019). Beyond the Bud: Emerging Methods of Cannabis Consumption for Youth. *Pediatr Clin North Am, 66*(6). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31679599

Tank, A., Tietz, T., Daldrup, T., Schwender, H., Hellen, F., Ritz-Timme, S., & Hartung, B. (2019). On the impact of cannabis consumption on traffic safety: a driving simulator study with habitual cannabis consumers. *Int J Legal Med, 133*(5). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/30701315

Thompson, R., DeJong, K., & Lo, J. (2019). Marijuana Use in Pregnancy: A Review. *Obstet Gynecol Surv, 74*(7). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31343707

van der Steur, S. J., Batalla, A., & Bossong, M. G. (2020). Factors Moderating the Association Between Cannabis Use and Psychosis Risk: A Systematic Review. *Brain Sci, 10*(2). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/32059350

Venkatesan, T., Levinthal, D. J., Li, B. U. K., Tarbell, S. E., Adams, K. A., Issenman, R. M., . . . Hasler, W. L. (2019). Role of chronic cannabis use: Cyclic vomiting syndrome vs cannabinoid hyperemesis syndrome. *Neurogastroenterol Motil, 31 Suppl 2*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31241817

Young-Wolff, K. C., Sarovar, V., Tucker, L. Y., Conway, A., Alexeeff, S., Weisner, C., . . . Goler, N. (2019). Self-reported Daily, Weekly, and Monthly Cannabis Use Among Women Before and During Pregnancy. *JAMA Netw Open, 2*(7). Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31322686

Young-Wolff, K. C., Sarovar, V., Tucker, L. Y., Goler, N., Conway, A., Weisner, C., . . . Alexeeff, S. (2019a). Validity of Self-reported Cannabis Use Among Pregnant Females in Northern California. *J Addict Med*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31688149

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