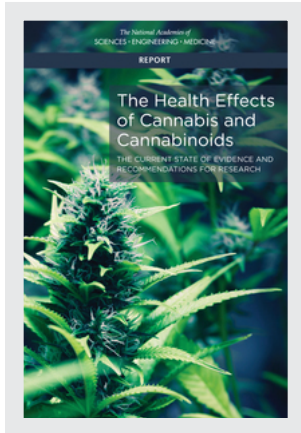


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The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research

DETAILS

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Summary

Over the past 20 years there have been substantial changes to the cannabis policy landscape. To date, 28 states and the District of Columbia have legalized cannabis for the treatment of medical conditions (NCSL, 2016). Eight of these states and the District of Columbia have also legalized cannabis for recreational use. These landmark changes in policy have markedly changed cannabis use patterns and perceived levels of risk. Based on a recent nationwide survey, 22.2 million Americans (12 years of age and older) reported using cannabis in the past 30 days, and between 2002 and 2015 the percentage of past month cannabis users in this age range has steadily increased (CBHSQ, 2016).

Despite the extensive changes in policy at the state level and the rapid rise in the use of cannabis both for medical purposes and for recreational use, conclusive evidence regarding the short- and long-term health effects (harms and benefits) of cannabis use remains elusive. A lack of scientific research has resulted in a lack of information on the health implications of cannabis use, which is a significant public health concern for vulnerable populations such as pregnant women and adolescents. Unlike other substances whose use may confer risk, such as alcohol or tobacco, no accepted standards exist to help guide individuals as they make choices regarding the issues of if, when, where, and how to use cannabis safely and, in regard to therapeutic uses, effectively.

Within this context, in March 2016, the Health and Medicine Division

BOX S-1
Statement of Task

The National Academies of Sciences, Engineering, and Medicine (the National Academies) will appoint an ad hoc committee to develop a comprehensive, in-depth review of existing evidence regarding the health effects of using marijuana and/or its constituents.

The committee will develop a consensus report with two primary sections: (1) a section of the report will summarize what can be determined about the health effects of marijuana use and, (2) a section of the report will summarize potential therapeutic uses of marijuana. The report will also provide a background overview of the cannabinoid/endocannabinoid system, history of use in the United States, and the regulation and policy landscape. In addition, the report will outline and make recommendations regarding a research agenda identifying the most critical research questions regarding the association of marijuana use with health outcomes (both risks and therapeutic) that can be answered in the short term (i.e., within a 3-year time frame) as well as any steps that should be taken in the short term to ensure that sufficient data are being gathered to answer long-term questions (e.g., appropriate questions on large population surveillance surveys, clinical data collection or other data capture, and resolution of barriers to linkage between survey data and death/morbidity registries to enable population-level morbidity and mortality effects estimates). The committee should focus on questions and consequences with the potential for the greatest public health impact, while shedding light on the characteristics of marijuana use that impact both short- and long-term health.

In conducting its work, the committee will conduct a comprehensive review of the evidence, using accepted approaches of literature search, evidence review, grading, and synthesis. Studies reviewed regarding health risks should be as broad as possible, including but not limited to epidemiology and clinical studies, and toxicology and animal studies when determined appropriate by the committee. The committee will provide summary determinations regarding causality based on strength of evidence. Both U.S. and international studies may be reviewed based upon relevance and methodological rigor.

(formerly the Institute of Medicine [IOM]¹) of the National Academies of Sciences, Engineering, and Medicine (the National Academies) was asked to convene a committee of experts to conduct a comprehensive review of the literature regarding the health effects of using cannabis and/or its constituents that had appeared since the publication of the 1999 IOM report

¹ As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously carried out by the Institute of Medicine (IOM).

Marijuana and Medicine. The resulting Committee on the Health Effects of Marijuana consisted of 16 experts in the areas of marijuana, addiction, oncology, cardiology, neurodevelopment, respiratory disease, pediatric and adolescent health, immunology, toxicology, preclinical research, epidemiology, systematic review, and public health. The sponsors of this report include federal, state, philanthropic, and nongovernmental organizations, including the Alaska Mental Health Trust Authority; Arizona Department of Health Services; California Department of Public Health; CDC Foundation; Centers for Disease Control and Prevention (CDC); The Colorado Health Foundation; Mat-Su Health Foundation; National Highway Traffic Safety Administration; National Institutes of Health/National Cancer Institute; National Institutes of Health/National Institute on Drug Abuse; Oregon Health Authority; the Robert W. Woodruff Foundation; Truth Initiative; U.S. Food and Drug Administration; and Washington State Department of Health.

In its statement of task, the committee was asked to make recommendations for a research agenda that will identify the most critical research questions regarding the association of cannabis use with health outcomes (both harms and benefits) that can be answered in the short term (i.e., within a 3-year time frame), as well as steps that should be taken in the short term to ensure that sufficient data are being gathered to answer long-term questions. Of note, throughout the report the committee has attempted to highlight research conclusions that affect certain populations (e.g., pregnant women, adolescents) that may be more vulnerable to potential harmful effects of cannabis use. The committee's full statement of task is presented in Box S-1.

STUDY CONTEXT AND APPROACH

Over the past 20 years the IOM published several consensus reports that focused on the health effects of marijuana or addressed marijuana within the context of other drug or substance abuse topics.² The two IOM reports that most prominently informed the committee's work were *Marijuana and Health*, published in 1982, and the 1999 report *Marijuana and Medicine: Assessing the Science Base*. Although these reports differed in scope, they were useful in providing a comprehensive body of evidence upon which the current committee could build.

The scientific literature on cannabis use has grown substantially since the 1999 publication of *Marijuana and Medicine*. The committee conducted an extensive search of relevant databases, including Medline, Embase,

² See <https://www.nap.edu/search/?year=1995&rpp=20&ft=1&term=marijuana> (accessed January 5, 2017).

BOX S-2
Health Topics and Prioritized Health Endpoints
(listed in the order in which they appear in the report)

Therapeutic effects

- Chronic pain; cancer, chemotherapy-induced nausea/vomiting; anorexia and weight loss; irritable bowel syndrome; epilepsy; spasticity related to multiple sclerosis or spinal cord injury; Tourette syndrome; amyotrophic lateral sclerosis; Huntington’s disease; Parkinson’s disease; dystonia; dementia; glaucoma; traumatic brain injury; addiction; anxiety; depression; sleep disorders; posttraumatic stress disorder; schizophrenia and other psychoses

Cancer

- Lung cancer; head and neck cancer; testicular cancer; esophageal cancer; other cancer

Cardiometabolic risk

- Acute myocardial infarction; stroke; metabolic dysregulation, metabolic syndrome, prediabetes, and diabetes mellitus

Respiratory disease

- Pulmonary function; chronic obstructive pulmonary disorder; respiratory symptoms (including chronic bronchitis); asthma

Immunity

- Immune function; infectious disease

the Cochrane Database of Systematic Reviews, and PsycINFO, and they initially retrieved more than 24,000 abstracts that could have potentially been relevant to this study. These abstracts were reduced by limiting articles to those published in English and removing case reports, editorials, studies by “anonymous” authors, conference abstracts, and commentaries. In the end, the committee considered more than 10,700 abstracts for their relevance to this report.

Given the large scientific literature on cannabis, the breadth of the statement of task, and the time constraints of the study, the committee developed an approach that resulted in giving primacy to recently published systematic reviews (since 2011) and high-quality primary research for 11 groups of health endpoints (see Box S-2). For each health endpoint,

Injury and death

- All-cause mortality; occupational injury; motor vehicle crash; overdose injury and death

Prenatal, perinatal, and postnatal exposure to cannabis

- Pregnancy complications for the mother; fetal growth and development; neonatal conditions; later outcomes for the infant

Psychosocial

- Cognition (learning, memory, attention, intelligence); academic achievement and educational outcomes; employment and income; social relationships and other social roles

Mental health

- Schizophrenia and other psychoses; bipolar disorders, depression; suicide; anxiety; posttraumatic stress disorder

Problem cannabis use

- Cannabis use disorder

Cannabis use and abuse of other substances

- Abuse of other substances

systematic reviews were identified and assessed for quality using published criteria; only fair- and good-quality reviews were considered by the committee. The committee's conclusions are based on the findings from the most recently published systematic review and all relevant fair- and good-quality primary research published after the systematic review. Where no systematic review existed, the committee reviewed all relevant primary research published between January 1, 1999, and August 1, 2016. Primary research was assessed using standard approaches (e.g., Cochrane Quality Assessment, Newcastle–Ontario scale) as a guide.

The search strategies and processes described above were developed and adopted by the committee in order to adequately address a broad statement of task in a limited time frame while adhering to the National

Academies' high standards for the quality and rigor of committee reports. Readers of this report should recognize two important points. First, the committee was not tasked to conduct multiple systematic reviews, which would have required a lengthy and robust series of processes. The committee did, however, adopt key features of that process: a comprehensive literature search; assessments by more than one person of the quality (risk of bias) of key literature and the conclusions; prespecification of the questions of interest before conclusions were formulated; standard language to allow comparisons between conclusions; and declarations of conflict of interest via the National Academies conflict-of-interest policies. Second, there is a possibility that some literature was missed because of the practical steps taken to narrow a very large literature to one that was manageable within the time frame available to the committee. Furthermore, very good research may not be reflected in this report because it did not directly address the health endpoint research questions that were prioritized by the committee.

This report is organized into four parts and 16 chapters. Part I: Introduction and Background, Part II: Therapeutic Effects (Therapeutic Effects of Cannabis and Cannabinoids), Part III: Other Health Effects, and Part IV: Research Barriers and Recommendations. In Part II, most of the evidence reviewed in Chapter 4 derives from clinical and basic science research conducted for the specific purpose of answering an a priori question of whether cannabis and/or cannabinoids are an effective treatment for a specific disease or health condition. The evidence reviewed in Part III derives from epidemiological research that primarily reviews the effects of smoked cannabis. It is of note that several of the prioritized health endpoints discussed in Part III are also reviewed in Part II, albeit from the perspective of effects associated with using cannabis for primarily recreational, as opposed to therapeutic, purposes.

Several health endpoints are discussed in multiple chapters of the report (e.g., cancer, schizophrenia); however, it is important to note that the research conclusions regarding potential harms and benefits discussed in these chapters may differ. This is, in part, due to differences in the study design of the reviewed evidence, differences in characteristics of cannabis or cannabinoid exposure (e.g., form, dose, frequency of use), and the populations studied. As such, it is important that the reader is aware that this report was not designed to reconcile the proposed harms and benefits of cannabis or cannabinoid use across the report's chapters. In drafting the report's conclusions, the committee made an effort to be as specific as possible about the type and/or duration of cannabis or cannabinoid exposure and, where relevant, cross-referenced findings from other report chapters.

REPORT CONCLUSIONS ON THE ASSOCIATION BETWEEN CANNABIS USE AND HEALTH

From their review, the committee arrived at nearly 100 different research conclusions related to cannabis or cannabinoid use and health. Informed by the reports of previous IOM committees,³ the committee developed standard language to categorize the weight of evidence regarding whether cannabis or cannabinoid use (for therapeutic purposes) is an effective or ineffective treatment for the prioritized health endpoints of interest, or whether cannabis or cannabinoid use (primarily for recreational purposes) is statistically associated with the prioritized health

³ *Adverse Effects of Vaccines: Evidence and Causality* (IOM, 2012); *Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence* (IOM, 2008); *Veterans and Agent Orange: Update 2014* (NASEM, 2016).

BOX S-3 Weight-of-Evidence Categories

CONCLUSIVE EVIDENCE

For therapeutic effects: There is strong evidence from randomized controlled trials to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence from randomized controlled trials to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are many supportive findings from good-quality studies with no credible opposing findings. A firm conclusion can be made, and the limitations to the evidence, including chance, bias, and confounding factors, can be ruled out with reasonable confidence.

SUBSTANTIAL EVIDENCE

For therapeutic effects: There is strong evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is strong evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good-quality studies with very few or no credible opposing findings. A firm conclusion can be made, but minor limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

continued

BOX S-3 Continued**MODERATE EVIDENCE**

For therapeutic effects: There is some evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is some evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are several supportive findings from good- to fair-quality studies with very few or no credible opposing findings. A general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out with reasonable confidence.

LIMITED EVIDENCE

For therapeutic effects: There is weak evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is weak evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are supportive findings from fair-quality studies or mixed findings with most favoring one conclusion. A conclusion can be made, but there is significant uncertainty due to chance, bias, and confounding factors.

NO OR INSUFFICIENT EVIDENCE TO SUPPORT THE ASSOCIATION

For therapeutic effects: There is no or insufficient evidence to support the conclusion that cannabis or cannabinoids are an effective or ineffective treatment for the health endpoint of interest.

For other health effects: There is no or insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and the health endpoint of interest.

For this level of evidence, there are mixed findings, a single poor study, or health endpoint has not been studied at all. No conclusion can be made because of substantial uncertainty due to chance, bias, and confounding factors.

endpoints of interest. Box S-3 describes these categories and the general parameters for the types of evidence supporting each category. For a full listing of the committee's conclusions, please see this chapter's annex.

REPORT RECOMMENDATIONS

This is a pivotal time in the world of cannabis policy and research. Shifting public sentiment, conflicting and impeded scientific research, and legislative battles have fueled the debate about what, if any, harms or benefits can be attributed to the use of cannabis or its derivatives. The committee has put forth a substantial number of research conclusions on the health effects of cannabis and cannabinoids. Based on their research conclusions, the committee members formulated four recommendations to address research gaps, improve research quality, improve surveillance capacity, and address research barriers. The report's full recommendations are described below.

Address Research Gaps

***Recommendation 1:* To develop a comprehensive evidence base on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), public agencies,⁴ philanthropic and professional organizations, private companies, and clinical and public health research groups should provide funding and support for a national cannabis research agenda that addresses key gaps in the evidence base. Prioritized research streams and objectives should include, but need not be limited to:**

Clinical and Observational Research

- Examine the health effects of cannabis use in at-risk or under-researched populations, such as children and youth (often described as less than 18 years of age) and older populations (generally over 50 years of age), pregnant and breastfeeding women, and heavy cannabis users.
- Investigate the pharmacokinetic and pharmacodynamic properties of cannabis, modes of delivery, different concentrations, in various populations, including the dose–response relationships of cannabis and THC or other cannabinoids.
- Determine the harms and benefits associated with understudied cannabis products, such as edibles, concentrates, and topicals.
- Conduct well-controlled trials on the potential beneficial and harmful health effects of using different forms of cannabis, such

⁴ Agencies may include the CDC, relevant agencies of the National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA).

as inhaled (smoked or vaporized) whole cannabis plant and oral cannabis.

- Characterize the health effects of cannabis on unstudied and understudied health endpoints, such as epilepsy in pediatric populations; symptoms of posttraumatic stress disorder; childhood and adult cancers; cannabis-related overdoses and poisonings; and other high-priority health endpoints.

Health Policy and Health Economics Research

- Identify models, including existing state cannabis policy models, for sustainable funding of national, state, and local public health surveillance systems.
- Investigate the economic impact of recreational and medical cannabis use on national and state public health and health care systems, health insurance providers, and patients.

Public Health and Public Safety Research

- Identify gaps in the cannabis-related knowledge and skills of health care and public health professionals, and assess the need for, and performance of, continuing education programs that address these gaps.
- Characterize public safety concerns related to recreational cannabis use and evaluate existing quality assurance, safety, and packaging standards for recreational cannabis products.

Improve Research Quality

Recommendation 2: To promote the development of conclusive evidence on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), agencies of the U.S. Department of Health and Human Services, including the National Institutes of Health and the Centers for Disease Control and Prevention, should jointly fund a workshop to develop a set of research standards and benchmarks to guide and ensure the production of high-quality cannabis research. Workshop objectives should include, but need not be limited to:

- The development of a minimum dataset for observational and clinical studies, standards for research methods and design, and guidelines for data collection methods.

- Adaptation of existing research-reporting standards to the needs of cannabis research.
- The development of uniform terminology for clinical and epidemiological cannabis research.
- The development of standardized and evidence-based question banks for clinical research and public health surveillance tools.

Improve Surveillance Capacity

Recommendation 3: To ensure that sufficient data are available to inform research on the short- and long-term health effects of cannabis use (both beneficial and harmful effects), the Centers for Disease Control and Prevention, the Substance Abuse and Mental Health Services Administration, the Association of State and Territorial Health Officials, National Association of County and City Health Officials, the Association of Public Health Laboratories, and state and local public health departments should fund and support improvements to federal public health surveillance systems and state-based public health surveillance efforts. Potential efforts should include, but need not be limited to:

- The development of question banks on the beneficial and harmful health effects of therapeutic and recreational cannabis use and their incorporation into major public health surveys, including the National Health and Nutrition Examination Survey, National Health Interview Survey, Behavioral Risk Factor Surveillance System, National Survey on Drug Use and Health, Youth Risk Behavior Surveillance System, National Vital Statistics System, Medical Expenditure Panel Survey, and the National Survey of Family Growth.
- Determining the capacity to collect and reliably interpret data from diagnostic classification codes in administrative data (e.g., *International Classification of Diseases-10*).
- The establishment and utilization of state-based testing facilities to analyze the chemical composition of cannabis and products containing cannabis, cannabinoids, or THC.
- The development of novel diagnostic technologies that allow for rapid, accurate, and noninvasive assessment of cannabis exposure and impairment.
- Strategies for surveillance of harmful effects of cannabis for therapeutic use.

Address Research Barriers

Recommendation 4: The Centers for Disease Control and Prevention, National Institutes of Health, U.S. Food and Drug Administration, industry groups, and nongovernmental organizations should fund the convening of a committee of experts tasked to produce an objective and evidence-based report that fully characterizes the impacts of regulatory barriers to cannabis research and that proposes strategies for supporting development of the resources and infrastructure necessary to conduct a comprehensive cannabis research agenda. Committee objectives should include, but need not be limited to:

- Proposing strategies for expanding access to research-grade marijuana, through the creation and approval of new facilities for growing and storing cannabis.
- Identifying nontraditional funding sources and mechanisms to support a comprehensive national cannabis research agenda.
- Investigating strategies for improving the quality, diversity, and external validity of research-grade cannabis products.

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ANNEX

Report Conclusions⁵*Chapter 4 Conclusions—Therapeutic Effects of Cannabis and Cannabinoids***There is conclusive or substantial evidence that cannabis or cannabinoids are effective:**

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

There is moderate evidence that cannabis or cannabinoids are effective for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)
- Improving symptoms of Tourette syndrome (THC capsules) (4-8)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
- Improving symptoms of posttraumatic stress disorder (nabilone; a single, small fair-quality trial) (4-20)

⁵ Numbers in parentheses correspond to chapter conclusion numbers.

There is limited evidence of a statistical association between cannabinoids and:

- Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage (4-15)

There is limited evidence that cannabis or cannabinoids are ineffective for:

- Improving symptoms associated with dementia (cannabinoids) (4-13)
- Improving intraocular pressure associated with glaucoma (cannabinoids) (4-14)
- Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone) (4-18)

There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:

- Cancers, including glioma (cannabinoids) (4-2)
- Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids) (4-4b)
- Symptoms of irritable bowel syndrome (dronabinol) (4-5)
- Epilepsy (cannabinoids) (4-6)
- Spasticity in patients with paralysis due to spinal cord injury (cannabinoids) (4-7b)
- Symptoms associated with amyotrophic lateral sclerosis (cannabinoids) (4-9)
- Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids) (4-10)
- Motor system symptoms associated with Parkinson's disease or the levodopa-induced dyskinesia (cannabinoids) (4-11)
- Dystonia (nabilone and dronabinol) (4-12)
- Achieving abstinence in the use of addictive substances (cannabinoids) (4-16)
- Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol) (4-21)

Chapter 5 Conclusions—Cancer

There is moderate evidence of *no* statistical association between cannabis use and:

- Incidence of lung cancer (cannabis smoking) (5-1)
- Incidence of head and neck cancers (5-2)

There is limited evidence of a statistical association between cannabis smoking and:

- Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking) (5-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Incidence of esophageal cancer (cannabis smoking) (5-4)
- Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi’s sarcoma, or bladder cancer (5-5)
- Subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use) (5-6)

Chapter 6 Conclusions—Cardiometabolic Risk

There is limited evidence of a statistical association between cannabis use and:

- The triggering of acute myocardial infarction (cannabis smoking) (6-1a)
- Ischemic stroke or subarachnoid hemorrhage (6-2)
- Decreased risk of metabolic syndrome and diabetes (6-3a)
- Increased risk of prediabetes (6-3b)

There is no evidence to support or refute a statistical association between *chronic effects* of cannabis use and:

- The increased risk of acute myocardial infarction (6-1b)

*Chapter 7 Conclusions—Respiratory Disease***There is substantial evidence of a statistical association between cannabis smoking and:**

- Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking) (7-3a)

There is moderate evidence of a statistical association between cannabis smoking and:

- Improved airway dynamics with acute use, but not with chronic use (7-1a)
- Higher forced vital capacity (FVC) (7-1b)

There is moderate evidence of a statistical association between the cessation of cannabis smoking and:

- Improvements in respiratory symptoms (7-3b)

There is limited evidence of a statistical association between cannabis smoking and:

- An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (occasional cannabis smoking) (7-2a)

There is no or insufficient evidence to support or refute a statistical association between cannabis smoking and:

- Hospital admissions for COPD (7-2b)
- Asthma development or asthma exacerbation (7-4)

*Chapter 8 Conclusions—Immunity***There is limited evidence of a statistical association between cannabis smoking and:**

- A decrease in the production of several inflammatory cytokines in healthy individuals (8-1a)

There is limited evidence of *no* statistical association between cannabis use and:

- The progression of liver fibrosis or hepatic disease in individuals with viral hepatitis C (HCV) (daily cannabis use) (8-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Other adverse immune cell responses in healthy individuals (cannabis smoking) (8-1b)
- Adverse effects on immune status in individuals with HIV (cannabis or dronabinol use) (8-2)
- Increased incidence of oral human papilloma virus (HPV) (regular cannabis use) (8-4)

Chapter 9 Conclusions—Injury and Death

There is substantial evidence of a statistical association between cannabis use and:

- Increased risk of motor vehicle crashes (9-3)

There is moderate evidence of a statistical association between cannabis use and:

- Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal (9-4b)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- All-cause mortality (self-reported cannabis use) (9-1)
- Occupational accidents or injuries (general, nonmedical cannabis use) (9-2)
- Death due to cannabis overdose (9-4a)

Chapter 10 Conclusions—Prenatal, Perinatal, and Neonatal Exposure

There is substantial evidence of a statistical association between maternal cannabis smoking and:

- Lower birth weight of the offspring (10-2)

There is limited evidence of a statistical association between maternal cannabis smoking and:

- Pregnancy complications for the mother (10-1)
- Admission of the infant to the neonatal intensive care unit (NICU) (10-3)

There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and:

- Later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use) (10-4)

Chapter 11 Conclusions—Psychosocial

There is moderate evidence of a statistical association between cannabis use and:

- The impairment in the cognitive domains of learning, memory, and attention (acute cannabis use) (11-1a)

There is limited evidence of a statistical association between cannabis use and:

- Impaired academic achievement and education outcomes (11-2)
- Increased rates of unemployment and/or low income (11-3)
- Impaired social functioning or engagement in developmentally appropriate social roles (11-4)

There is limited evidence of a statistical association between *sustained abstinence from cannabis use* and:

- Impairments in the cognitive domains of learning, memory, and attention (11-1b)

*Chapter 12 Conclusions—Mental Health***There is substantial evidence of a statistical association between cannabis use and:**

- The development of schizophrenia or other psychoses, with the highest risk among the most frequent users (12-1)

There is moderate evidence of a statistical association between cannabis use and:

- Better cognitive performance among individuals with psychotic disorders and a history of cannabis use (12-2a)
- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use) (12-4)
- A small increased risk for the development of depressive disorders (12-5)
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users (12-7a)
- Increased incidence of suicide completion (12-7b)
- Increased incidence of social anxiety disorder (regular cannabis use) (12-8b)

There is moderate evidence of *no* statistical association between cannabis use and:

- Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders (12-2c)

There is limited evidence of a statistical association between cannabis use and:

- An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders (12-2b)
- The likelihood of developing bipolar disorder, particularly among regular or daily users (12-3)
- The development of any type of anxiety disorder, except social anxiety disorder (12-8a)
- Increased symptoms of anxiety (near daily cannabis use) (12-9)

- Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)

There is no evidence to support or refute a statistical association between cannabis use and:

- Changes in the course or symptoms of depressive disorders (12-6)
- The development of posttraumatic stress disorder (12-10)

Chapter 13 Conclusions—Problem Cannabis Use

There is substantial evidence that:

- Stimulant treatment of attention deficit hyperactivity disorder (ADHD) during adolescence is *not* a risk factor for the development of problem cannabis use (13-2e)
- Being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use (13-2i)
- Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use (13-2j)

There is substantial evidence of a statistical association between:

- Increases in cannabis use frequency and the progression to developing problem cannabis use (13-1)
- Being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does not differ between males and females (13-3b)

There is moderate evidence that:

- Anxiety, personality disorders, and bipolar disorders are *not* risk factors for the development of problem cannabis use (13-2b)
- Major depressive disorder is a risk factor for the development of problem cannabis use (13-2c)
- Adolescent ADHD is *not* a risk factor for the development of problem cannabis use (13-2d)

- Being male is a risk factor for the development of problem cannabis use (13-2f)
- Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use (13-2g)
- Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use (13-2h)
- During adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, anti-social behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use (13-2k)

There is moderate evidence of a statistical association between:

- A persistence of problem cannabis use and a history of psychiatric treatment (13-3a)
- Problem cannabis use and increased severity of posttraumatic stress disorder symptoms (13-3c)

There is limited evidence that:

- Childhood anxiety and childhood depression are risk factors for the development of problem cannabis use (13-2a)

Chapter 14 Conclusions—Cannabis Use and the Abuse of Other Substances

There is moderate evidence of a statistical association between cannabis use and:

- The development of substance dependence and/or a substance abuse disorder for substances, including alcohol, tobacco, and other illicit drugs (14-3)

There is limited evidence of a statistical association between cannabis use and:

- The initiation of tobacco use (14-1)
- Changes in the rates and use patterns of other licit and illicit substances (14-2)

Chapter 15 Conclusions—Challenges and Barriers in Conducting Cannabis Research

There are several challenges and barriers in conducting cannabis and cannabinoid research, including

- There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research (15-1)
- It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use (15-2)
- A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use (15-3)
- To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed (15-4)

Part I

Introduction and Background

