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Understanding the Health Effects of Recreational Cannabis Use

A Focused Practice Question

Region of Peel – Public Health

Chronic Disease and Injury Prevention Division &
Family Health Division

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Key Messages

1. It is difficult to draw firm conclusions on the health effects of recreational cannabis use due to mixed findings and limitations in the evidence. Most studies are observational, and there are inconsistencies in assessing exposure and/or controlling for confounding variables. More research is needed.

2. The evidence is strongest for the associations between:

    - Cannabis use and respiratory symptoms and bronchitis, motor vehicle crashes, and schizophrenia or other psychoses.

    - Earlier and more frequent cannabis use and the risk for problem cannabis use.

3. Firm conclusions cannot be made for cannabis use and other health outcomes, including cancer and maternal and child health, due to lack of research, inconsistent findings, and/or weak evidence.

1 Issue & Context

In October 2018, Canada legalized cannabis for recreational use. As only the second country to legalize cannabis at a national level, this policy change has been coupled with uncertainties, including the specific impacts on public safety and population health. All levels of government have a role within the legislative framework for cannabis. Municipalities play a key role in implementation and enforcement.

Under the *Ontario Public Health Standards: Requirements for Programs, Services, and Accountability (2018)*, public health units are required to use a comprehensive health promotion approach to reduce the burden of cannabis use, among other substances, within their communities.[1] A core part of this approach involves supporting the public in making informed decisions regarding its potential use. Providing relevant and reliable health information is fundamental to this work, particularly as regulations and policies continue to develop.

In 2015/2016, eight per cent of the Peel population aged 12 years and older reported using cannabis at least once in the past year, which is significantly lower than the provincial estimate (12 per cent).[A] In 2017, 16 per cent of students between grades seven to 12 reported using cannabis at least once in the past year, which is similar to the provincial estimate (19 per cent).[B] National data from the initial months following legalization demonstrate an increase in cannabis use. Among Canadians aged 15 years and older, there was an increase in cannabis use in the past three months when comparing the first quarter of 2019 (18 per cent) to the same period in the previous year (14 per cent).[2] In Ontario, specifically, the prevalence increased to 20 per cent in the first quarter of 2019 compared to 14 per cent in the same period in the previous year.[2]

Continued monitoring of consumption levels and related behaviours is needed to understand the long-term impacts of legalization.

The need for health messaging is underscored by requests internally and from the community. Over the last several months, the Region of Peel – Public Health (ROP-PH) received inquiries from Family Health staff and partners, including school boards and area municipalities, regarding the health effects of cannabis use.

In alignment with public health's mandate, and in response to local need, ROP-PH seeks to understand the health impacts, including the risks and benefits, of recreational cannabis use. This will inform the development of key messages, which will be shared with the public and other stakeholders, including health professionals and educators.

2 Literature Review Question

What are the physical, mental and social health effects of recreational cannabis use?

3 Literature Search

In August 2018, a librarian and an analyst conducted a search of published and grey literature. Databases included EBM Reviews-Cochrane Database of Systematic Reviews, Global Health, Ovid Healthstar, Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, PsycINFO, Cumulative Index of Nursing and Allied Health Literature (CINAHL) and SocINDEX.

Grey-literature sources included Substance Abuse and Mental Health Services Administration (SAMHSA), National Institute on Drug Abuse (NIDA), Centre for Addiction and Mental Health (CAMH), Canadian Centre on Substance Use and Addiction (CCSUA), National Institute for Health and Care Excellence (NICE) Evidence, NICE Guidance, National Guideline Clearinghouse (NGC), Health Canada, Public Health Ontario (PHO), World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), Google and Turning Research into Practice (TRIP) Medical Database.

The search was limited to review of reviews or guidelines that were published in English language and within the past five years. These limits were applied as the team was aware of recent highly synthesized evidence on the topic. It was also to reduce the volume of evidence reviewed within the short time frame for this project. An academic partner was consulted for advice on creating the "review of reviews" search filter used in the search strategy. See Appendix A.

4 Relevance Assessment

Documents were assessed for relevance based on the following criteria:

- Inclusion criteria: guidelines or review of reviews; general population; recreational exposure to any form of cannabis; positive or negative physical, mental, or social health effects of cannabis use; English language; published within the last five years.

- Exclusion criteria: duplicate or overlap; cannabis use for medical purposes (i.e., cannabis use as a treatment for medical conditions); exposure to synthetic cannabis (e.g., "Spice",

"K2") or a pharmaceutical product (e.g., Sativex®); clinical management or treatment of cannabis use or cannabis use disorders.

One reviewer screened the titles and abstract of all identified literature (i.e., first-level relevance assessment). A second reviewer screened potentially relevant documents (i.e., second-level relevance assessment). Discrepancies were resolved through discussion until consensus was reached.

Three reviewers independently screened the documents carried to full-text review. Discrepancies were resolved through discussion until consensus was reached or in consultation with a fourth reviewer.

5 Results of the Search

The literature search identified 786 results. Three hundred fifteen documents were carried to first-level relevance assessment, of which 275 were excluded. Forty documents were carried to second-level relevance assessment, of which nine were excluded. Thirty-one documents were assessed in full, of which 24 were excluded. Six review of reviews and one guideline were deemed relevant. An additional review of reviews was published after the literature search was completed. This document was deemed relevant. See Appendix B.

6 Critical Appraisal

Two reviewers independently critically appraised the seven review of reviews and one guideline using the Health Evidence™ Quality Assessment tool and Agree II appraisal tool, respectively.

Discrepancies were resolved through discussion until consensus was reached or in consultation with a third reviewer. Two review of reviews were rated strong, one was rated moderate and four were rated weak. The four weak-rated documents were excluded. The guideline was rated lower quality (3/7; use with modifications).

An overlap assessment was conducted of the remaining three review of reviews and one guideline. Two review of reviews had a high degree of overlap between the included articles. Of these, the review of reviews that focused on only one specific health outcome was excluded.[3]

7 Description of Included Documents

Two review of reviews and one guideline were included. See Appendix C.

The National Academies of Sciences, Engineering and Medicine (2017): The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research.[4]

This strong-quality review of reviews examined the health consequences of using cannabis or its constituents. It provided recommendations on the most critical research questions to be answered in the short- and long-term, and what is required to address those questions. The report was not intended to be a systematic review; however, the authors adopted key features of the review process.

The review of reviews did not focus on a particular population; however, specific groups were discussed (e.g. mothers and offspring in the chapter on prenatal, perinatal and neonatal cannabis exposure). Different forms of cannabis use were considered, although the authors noted that most evidence examined cannabis smoking. Eleven health topics related to

therapeutic and non-therapeutic use were included: therapeutic effects; cancer; cardiometabolic risk; respiratory disease; immunity; injury and death; effects from prenatal, perinatal, and postnatal exposure; psychosocial effects; mental health; problem cannabis use; abuse of other substances. More specific outcomes were explored within each health topic.

A general methodology for identifying and synthesizing the evidence was used; deviations to the process were noted within specific chapters of the document. A search for articles published between January 1999 to August 2016 was conducted. Systematic reviews and primary literature were included; however, the specific number and types of articles were not stated. Primary literature included "peer-reviewed cross-sectional studies, case-control studies, cohort studies, randomized controlled trials, or non-systematic literature reviews."[4] The authors prioritized recent good- or fair-quality systematic reviews for each health topic, and included primary literature published after the search date limits of the systematic review(s). Systematic reviews were critically appraised based on: study eligibility criteria, identification and collection of studies, data collection and study appraisal, synthesis and findings, and conflict of interest. Primary literature were critically appraised using the Cochrane Quality Assessment and Newcastle-Ontario scale. Results from the critical appraisal were not provided; however, only good- or fair-quality systematic reviews and primary research literature were used. The authors graded the strength of available evidence according to five categories:

- **Conclusive evidence:** "There is strong evidence from randomized controlled trials to support or refute a statistical association…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."[4(p.S-5)]

- **Substantial evidence:** "There is strong evidence to support or refute a statistical association…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."[4(p.S-5,6)]
- **Moderate evidence:** "There is some evidence to support or refute a statistical association…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."[4(p.S-6)]
- **Limited evidence:** "There is weak evidence to support or refute a statistical association…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."[4(p.S-6)]
- **No or insufficient evidence:** "There is no or insufficient evidence to support or refute a statistical association… There are mixed, a single poor study, or health endpoint has not been studied at all. No conclusions can be made because of substantial uncertainty due to chance, bias, and confounding factors."[4(p.S-6)]

These categories reflect the quality, quantity and consistency of the body of evidence that support a conclusion.

Due to the volume of evidence in this report, supporting data were not extracted by the review team for health outcomes with "limited" or "no or insufficient" evidence gradings.

Fischer et al. (2017): Lower-risk cannabis use guidelines: A comprehensive update of evidence and recommendations.[5]

As an update to a 2011 publication,[6] this lower-quality guideline provided recommendations for lowering the risk of harms from cannabis use. It included a review of evidence on modifiable cannabis use behaviours that determine adverse health outcomes.

The guideline targeted cannabis users in general, but also provided information on special-risk populations, including pregnant women and individuals who are predisposed to mental health or substance use disorders. Various cannabis exposures were discussed, including different use behaviours and the use of different cannabis products. A range of adverse health outcomes were reviewed, including brain function, mental health and respiratory disease. For a full list of health outcomes, see page 87 in Appendix C.

The authors primarily searched for systematic reviews and meta-analyses that were published between January 2010 to December 2016. The specific number and types of included articles were not stated, although the reference list included reviews and single studies. Critical appraisal methods were not described, although the authors reported using a grading scheme to assess the strength of evidence behind each cannabis use recommendation. The strength-of-evidence categories were the same as those used within the National Academies of Sciences, Engineering and Medicine (2017) report described above (i.e., conclusive, substantial, moderate, limited, none or insufficient).[4]

Ontario Agency for Health Protection and Promotion (Public Health Ontario). (2018): Evidence brief: Health effects of cannabis exposure in pregnancy and breastfeeding.[7]

This strong-quality review of reviews assessed child and youth outcomes associated with exposure to maternal cannabis use during preconception, pregnancy or breastfeeding. It also provided clinical recommendations for practitioners that care for reproductive-age, pregnant or breastfeeding women who may use cannabis.

The review of reviews focused on pregnant women and offspring (i.e., infants, children and youth) of mothers who used cannabis during pregnancy or while breastfeeding. Specific forms of cannabis use were not stated. A range of maternal, infant, child and youth outcomes were considered, though only select outcomes were reported in the evidence brief. Examples of outcomes include maternal anaemia, low birth weight and preterm delivery. For a full list of health outcomes, see page 94 in Appendix C.

The authors searched for articles published between 2006 and April 2018. Eleven articles were included within the review of reviews; six systematic reviews (three with meta-analyses) and five guidelines. Critical appraisal of included documents was completed using the Health Evidence™ Quality Assessment Tool for systematic reviews and AGREE II appraisal tool for guidelines. All included systematic reviews and guidelines were strong or moderate quality. Within the systematic reviews, component studies ranged from moderate to very low quality.

8 Synthesis of Findings

In synthesizing evidence from the three included documents,[4,5,7] greater weighting was placed on the National Academies of Sciences, Engineering and Medicine (2017) report.[4] It was the most comprehensive and closely aligned to the research question. It also provided graded conclusion statements for each health outcome. Within the current Focused Practice Question,

there are certain health outcomes for which the body of evidence was small and not graded. The review team drew conclusions from what evidence was available at the time of evidence review development.

A synthesis of findings from the three included documents is provided below:

It is difficult to draw firm conclusions on the health effects of recreational cannabis use due to limitations in the evidence, including those that stem from observational study designs.

More research on the health effects of cannabis use is needed. Most of the evidence is based on observational studies,[4] including cross-sectional and naturalistic studies.[5] Within observational research on cannabis, exposure assessments are a key challenge:

- Self-reporting is the most common method of assessing exposure.[4,7] This may introduce social desirability bias and underestimate results, especially when considering the illicit status of cannabis in many jurisdictions.[4,7]
- It is difficult to accurately assess cannabis exposure, including the dose, specific type of cannabis product used or mode of intake. This presents variability in how cannabis exposure is defined across studies.[4]
- Studies on cannabis use may be confounded by poly-substance use, such as tobacco use.[4,7] This obscures the ability to determine whether observed health effects are truly a result of cannabis use.[4]

Other challenges with observational research on cannabis include poor controlling for other confounding variables,[7] variation in the populations examined within reviews,[4] and inconsistent reporting of methods within reviews.[4]

Additional limitations of the evidence include the lack of longitudinal assessments[4] and use of small study cohorts.[4] The use of outdated cohort data may affect the applicability of findings due to changes in cannabis potency over the decades.[7]

Cancer

Cannabis smoking may not be associated with lung cancer.

There is moderate evidence that cannabis smoking is not associated with the incidence of lung cancer.[4] This is primarily based on a meta-analysis that found habitual cannabis smokers did not have a higher odds of lung cancer compared to non-habitual cannabis smokers (odds ratio (OR): 0.96, 95% confidence interval (CI): 0.66 to 1.38).[4] Habitual cannabis smokers are defined as those having a cumulative cannabis consumption of at least one joint-year (i.e., smoking one joint per day for one year).[8] Primary literature show mixed results on the presence of an association between cannabis smoking and lung cancer.[4,5] Positive associations are inconclusive largely due to confounding by tobacco use.[5]

Cannabis use may not be associated with head and neck cancers.

There is moderate evidence that cannabis use is not associated with the incidence of head and neck cancers.[4] This is based on a meta-analysis that found no association between cannabis use and head and neck cancers when analyzed as a group, and adjusted for tobacco use, age, gender and race (adjusted odds ratio (aOR): 1.021, 95% CI: 0.912 to 1.143).[4] The available evidence did not examine associations between cannabis use and specific head and neck cancers on their own.[4]

There is uncertainty on the association between cannabis use and other cancers, including cancers in offspring.

There is limited evidence that current, frequent or chronic cannabis smoking is associated with non-seminoma-type testicular germ cell tumours.[4] There is insufficient evidence on whether parental cannabis use is associated with the risk of developing cancers in offspring.[4] This includes cancers such as acute myeloid leukemia, acute lymphoblastic leukemia and neuroblastoma.[4] Although case-control studies have found associations between maternal cannabis use and cancers in offspring, they provide weak evidence for causal associations.[5] There is insufficient evidence on whether cannabis smoking is associated with esophageal cancer, and on whether cannabis use is associated with prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer.[4]

Cardiometabolic Risk

There is uncertainty on the association between cannabis smoking or the chronic effects related to cannabis use and acute myocardial infarction.

There is limited evidence that cannabis smoking is associated with triggering acute myocardial infarction.[4] There is no evidence on whether the chronic effects of cannabis use are associated with the risk of acute myocardial infarction.[4]

There is uncertainty on the association between cannabis use and stroke.

There is limited evidence that cannabis use is associated with ischemic stroke or subarachnoid hemorrhage.[4]

There is uncertainty on the association between cannabis use and metabolic syndrome, diabetes and pre-diabetes.

There is limited evidence that cannabis use is associated with a decreased risk of metabolic syndrome and diabetes, or an increased risk of pre-diabetes.[4]

Respiratory Disease

Cannabis smoking is associated with respiratory symptoms and bronchitis.

There is substantial evidence that long-term cannabis smoking is associated with worse respiratory symptoms and more frequent episodes of chronic bronchitis.[4] This is informed by a systematic review that found long-term cannabis smoking worsens respiratory issues such as cough (OR: 1.7 to 2.0, CIs not stated), sputum production (OR: 1.5 to 1.9, CIs not stated) and wheeze (OR: 2.0 to 3.0, CIs not stated).[4] The findings are similar to the results of other systematic reviews and primary studies.[4,5] Other respiratory problems associated with cannabis use include acute pharyngitis, dyspnea, hoarse voice, worse cystic fibrosis symptoms and chest tightness.[4] Acute and chronic bronchitis have been linked with cannabis smoking.[4,5] The risk of respiratory problems may increase with more intensive use.[5]

Respiratory problems may be reversed after the cessation of cannabis smoking.[4,5] There is moderate evidence that the cessation of cannabis smoking is associated with improvements in respiratory symptoms.[4] This was informed by several primary studies, one of which found that compared to former cannabis users, current users were more likely to have cough (OR: 3.3, CI not stated), sputum production (OR: 4.2, CI not stated) or wheeze (OR: 2.1, CI not stated).[4]

There is uncertainty on the association between cannabis smoking and chronic obstructive pulmonary disease (COPD).

After controlling for tobacco use, there is limited evidence that occasional cannabis smoking is associated with an increased risk of developing COPD.[4] There is insufficient evidence on whether cannabis smoking is associated with hospital admissions for COPD.[4] One document noted the presence of emphysematous lung bullae in young cannabis smokers.[5] The authors stated that these findings are uncertain.[5]

There is uncertainty on the association between cannabis smoking and asthma.

There is no or insufficient evidence on whether cannabis smoking is associated with asthma development or exacerbation.[4]

Immunity

There is uncertainty on the association between cannabis use and immune function.

Among healthy individuals, there is limited evidence that cannabis smoking is associated with a decrease in the production of several inflammatory cytokines, or with other adverse immune cell responses.[4] Among individuals with human immunodeficiency virus (HIV), there is insufficient evidence on whether cannabis use is associated with adverse effects on immune status.[4] Among individuals with viral Hepatitis C (HCV), there is limited evidence that daily cannabis use is not associated with the progression of liver fibrosis or hepatic disease.[4] There is insufficient evidence on whether regular cannabis use is associated with increased incidence of oral human papilloma virus (HPV).[4]

Injury and Death

Cannabis use is associated with an increased risk of motor vehicle crashes (MVCs).

Cannabis use acutely impairs functions that are important for driving in a dose-dependent way.[5] These functions include cognition, attention, memory, decision-making and psychomotor functioning.[5] The degree and duration of impairment depends on various factors, including those related to the individual, the product and use behaviour.[5] Cannabis use increases the risk of MVC.[4,5] One document reviewed six systematic reviews and concluded that there is substantial evidence that cannabis use is associated with an increased risk of MVCs.[4] The conclusion was primarily based on the most recent meta-analysis which found driving under the influence of cannabis increases the odds of MVCs by as little as 22 per cent or as high as 36 per cent (OR: 1.22, 95% CI: 1.10 to 1.36; OR: 1.36, 95% CI: 1.15 to 1.61), depending on the analytic technique.[4] In a subgroup analysis within the review, the odds of an MVC were lowered when alcohol intoxication was accounted for (OR: 1.11, 95% CI: 1.04 to 1.18; OR: 1.18, 95% CI: 1.07 to 1.30). The odds were increased when alcohol intoxication was not accounted for (OR: 1.79, 95% CI: 1.28 to 2.51; OR: 1.69, 95% CI: 1.25 to 2.28).[4] The risk of MVCs may be increased with earlier onset of cannabis use, more frequent use, the co-use with alcohol, or the use of more potent products.[5]

Cannabis use, particularly the use of ingested products, may be associated with an increased risk of overdose injuries. There is uncertainty on the association between cannabis use and death due to cannabis overdose.

The use of ingested cannabis products contributes to overdose risk as the delayed absorption and onset of psychoactive effects may result in overconsumption.[5] These products may also be

accidentally ingested by children.[5] Among children in U.S. states where cannabis is legal, there is moderate evidence that cannabis use is associated with an increased risk of overdose injuries.[4] This is based on primary literature that found increases in poison control center calls and hospitalizations for unintentional pediatric exposure to cannabis.[4] These increases followed changes to cannabis policy, including the legalization of recreational cannabis.[4] Symptoms of overdose injuries include lethargy, ataxia, dizziness, respiratory insufficiency and agitation.[4] More serious, but less common symptoms, include coma, cardiovascular symptoms and respiratory depression.[4]

There is insufficient evidence on whether cannabis use is associated with deaths due to cannabis overdose.[4]

There is uncertainty on the association between cannabis use and all-cause mortality.

There is insufficient evidence on whether self-reported cannabis use is associated with all-cause mortality.[4]

There is uncertainty on the association between cannabis use and occupational accidents or injuries.

There is insufficient evidence on whether general, non-medical cannabis use is associated with occupational accidents or injuries.[4]

Maternal and Child Outcomes

There is uncertainty on the association between cannabis use during pregnancy and maternal anemia.

Some evidence suggests cannabis use during pregnancy is associated with maternal anaemia.[5] This is based on a meta-analysis that found a significant increase in odds of anemia in pregnant women who used cannabis during pregnancy (OR: 1.4, 95% CI: 1.1 to 1.7).[5] However, it was noted in another document that the meta-analysis did not control for polysubstance use.[7]

There is uncertainty on the association between cannabis use during pregnancy and low birth weight.

Some evidence suggests cannabis use during pregnancy is associated with infant low birth weight.[4,5] These conclusions are based on a meta-analysis which found in utero exposure to cannabis is associated with lower birth weight among infants exposed to cannabis in pregnancy compared to those not exposed (OR: 1.77, 95% CI: 1.04 to 3.01; mean difference (MD): -109.42g, 95% CI: -38.72g to -180.12g).[4,5] However, it was noted in another document that the meta-analysis did not control for poly-substance use.[7] A more recent meta-analysis found cannabis use during pregnancy increased the risk for low birth weight (relative risk (RR): 1.43, 95% CI: 1.27 to 1.62).[7] This estimate became statistically insignificant after controlling for confounders (i.e., tobacco use and other substances, socioeconomic and demographic factors).[7] Supporting data were not provided for the adjusted analysis. It was also noted that the meta-analysis may have been underpowered to detect significant differences due to small sample sizes.[7] Similarly, primary studies provided inconsistent evidence on the association between cannabis use during pregnancy and low birth weight,[5] depending on ability to control for other drug use (i.e., cocaine and opiates).[4]

There is uncertainty on the association between cannabis use during pregnancy and infant admission to neonatal intensive care unit (NICU).

Some evidence suggests cannabis use in pregnancy is associated with infant admission to NICU.[4,5] A meta-analysis found increased odds of NICU admission among infants exposed to cannabis in pregnancy compared to those not exposed (OR: 2.02, 95% CI: 1.27 to 3.21).[5] However, another document noted that this meta-analysis did not control for poly-substance use.[7]

There is uncertainty on the association between cannabis use during pregnancy and preterm delivery.

In one document, a meta-analysis found cannabis use during pregnancy increased the risk for preterm delivery (RR: 1.32, 95% CI: 1.14 to 1.54).[7] This estimate became statistically insignificant after controlling for confounders such as the use of tobacco and other substances, as well as socioeconomic and demographic factors.[7] Supporting data were not provided for the adjusted analysis. It was also noted that the meta-analysis may have been underpowered to detect significant differences due to small sample sizes.[7] Overall, the document concluded there is inconsistent evidence on the association between maternal cannabis use and preterm delivery, depending on the ability to control for tobacco use.[7]

There is uncertainty on the association between cannabis use during pregnancy and stillbirth, spontaneous abortion, fetal distress and other pregnancy complications.

There is limited evidence that maternal cannabis smoking is associated with stillbirth, spontaneous abortion, fetal distress or other pregnancy complications.[4]

There is uncertainty on the association between cannabis use during pregnancy and conduct problems in offspring.

There is insufficient evidence on whether cannabis use during pregnancy is associated with conduct problems in offspring.[4] One document suggested that maternal cannabis use may be associated with child development and behaviour problems.[5] Another document reported that a meta-analysis did not find an association between cannabis use in pregnancy and conduct problems in children or youth (OR: 1.29, 95% CI: 0.93 to 1.81).[7] However, the included studies were of poor quality and authors of the meta-analysis stated that there is insufficient evidence to draw conclusions.[7]

There is uncertainty on the association between cannabis use during pregnancy and school performance, and academic achievement in offspring.

There is insufficient evidence on whether maternal cannabis use is associated with cognition/academic achievement in offspring.[4] It has been suggested that maternal use could be associated with poor school performance in children.[5]

There is uncertainty on the association between cannabis use during pregnancy and substance use, and delinquency in offspring.

There is insufficient evidence on whether maternal cannabis smoking is associated with substance use and delinquency in offspring.[4] It has been suggested that maternal cannabis use could be associated with illicit drug use in children.[5]

There is uncertainty on the association between cannabis use during pregnancy and sudden infant death syndrome (SIDS), breastfeeding, physical growth, or mental health and psychosis in offspring.

There is insufficient evidence on whether maternal cannabis smoking is associated with SIDS, breastfeeding, physical growth, or mental health and psychosis in offspring.[4]

There is uncertainty on the association between cannabis use when breastfeeding and mental and motor development at one year of age, physical growth and SIDS in offspring.

One document found cannabis use during breastfeeding is not associated with mental and motor development at one year of age, physical growth and SIDS in the offspring.[7] Supporting data were not provided. Overall, this document concluded there is limited evidence on the association between maternal cannabis use and neonatal, behavioural and neurocognitive outcomes in offspring.[7]

Psychosocial

Acute cannabis use may be associated with cognitive impairments. There is uncertainty on whether these impairments are sustained after a period of abstinence.

There is moderate evidence that acute cannabis use is associated with impairments in learning, memory and attention.[4] There is limited evidence that sustained abstinence from cannabis use is associated with impairments in these cognitive domains.[4] These conclusions are based on several systematic reviews cited within one document:

- **Learning:** One review found strong support for the acute impact of cannabis use on learning.[4] Three reviews found mixed, little or no support for the sustained impact of cannabis use on learning after cessation.[4]
- **Memory:** One review found moderate-to-strong support for the acute impact of cannabis use on memory.[4] Three reviews found mixed or no support for the sustained impact after cessation.[4] Among the three reviews examining the sustained impact of cannabis use on memory, two noted that cannabis users may employ different parts of the brain (i.e., compensatory efforts) to achieve equivalent task performance as non-users.[4]
- **Attention:** One review found strong support for the acute impact of cannabis use on attention.[4] Four reviews found mixed, limited or no support for the sustained impact of cannabis use on attention after cessation.[4] Among the three reviews examining the sustained impact of cannabis use on attention, one noted that cannabis users may employ compensatory efforts to achieve equivalent task performance as non-users.[4]

The risk for negative cognitive outcomes may be increased with early onset, more frequent or intensive use, or use of potent products.[5] Among frequent or chronic cannabis users, tolerance effects may reduce cognitive impairment.[5]

There is uncertainty on the association between cannabis use and impaired academic achievement and education outcomes.

There is limited evidence that cannabis use is associated with impaired academic achievement and education outcomes.[4,5] It has been suggested that earlier onset and more frequent use could be associated with increased risk for poorer education outcomes, including high school

and degree completion.[5] This risk may be increased depending on earlier onset and more frequent use.[5]

There is uncertainty on the association between cannabis use and increased rates of unemployment and/or low income.

There is limited evidence that cannabis use is associated with increased rates of unemployment and/or low income.[4]

There is uncertainty on the association between cannabis use and impaired social functioning or engagement in developmentally appropriate social roles.

One document concluded that there is limited evidence that cannabis use is associated with impaired social functioning or engagement in developmentally appropriate social roles.[4] This is primarily based on results from a systematic review which noted that impacts on social functioning can take on different forms, including anti-social behaviours, offending, and contact with police.[4] It has been suggested that earlier onset of cannabis use may increase the risk for behavioural impulsivity.[5]

Mental Health

Co-morbidity between substance use and mental health disorders is not uncommon.[4] Possible explanations for this include:[4]

- Substance use may be a risk factor for mental health disorders.
- Mental health disorders may be a risk factor for substance use disorders.
- Mental health and substance use disorders may share the same risk factors (e.g., genetics, environment).

This affects the ability to determine directionality in the relationship between substance use and mental health outcomes.[4]

Cannabis use is associated with the development of schizophrenia or other psychoses.

There is substantial evidence that cannabis use is associated with the development of schizophrenia or other psychoses.[4] This conclusion is primarily based on two systematic reviews out of five reviews that were identified.[4] Both were meta-analyses and found a relationship between cannabis use and psychotic outcomes, with one meta-analysis identifying an increased odds of 3.59 (95% CI: 2.42 to 5.32) for psychotic symptoms and 5.07 (95% CI: 3.62 to 7.09) for a diagnosis of schizophrenia or psychotic disorder.[4] A dose-response relationship may also exist.[4] One of the meta-analyses found that the odds of developing psychosis are greater for users at median dose (OR: 1.97, 95% CI: 1.68 to 2.31) and users with a dose in the top 20 per cent (OR: 3.40, 95% CI: 2.55 to 4.54).[4] The other meta-analysis found that individuals that have ever used cannabis had increased odds of a psychotic outcome (aOR: 1.41, 95% CI: 1.20 to 1.65), with an increased frequency of use contributing to an even greater odds (aOR 2.09, 95% CI: 1.54 to 2.84).[4] Individual studies within this pooled analysis adjusted for confounders. Within primary studies, the presence of an association between cannabis use and psychotic outcomes were mixed.[4] The risk for developing psychotic symptoms is increased with early onset,[5] more frequent[4,5] and intensive[5] use, or the use of potent products.[5] Individuals with a family history of psychosis or who are genetically predisposed may be at increased risk.[5]

Among individuals with psychotic disorders, there is moderate evidence that cannabis use is not associated with the worsening of negative symptoms of schizophrenia.[4] Examples of negative symptoms include diminished emotional expression, lack of interest or motivation in social engagement, speech disturbance or anhedonia.[4] This was primarily based on a systematic

review which found that cannabis use is not associated with negative symptoms in most of its included studies.[4] The majority of other primary studies similarly found no association between cannabis use and differences in negative symptoms.[4]

Among individuals with psychotic disorders, there is limited evidence that cannabis use is associated with an increase in positive symptoms.[4] Positive symptoms potentially include delusions, hallucinations, or abnormal motor behaviour.[4]

Among individuals with psychotic disorders, there is moderate evidence that a history of cannabis use is associated with enhanced cognitive performance.[4] This was primarily based on three meta-analyses which found that compared to non-users, patients who used cannabis performed better on certain measures of cognition, such as global cognition and processing speed.[4] The results were mixed for other cognitive test measures, including attention and memory.[4] Primary studies demonstrate inconsistent findings, with studies finding either no association between cannabis use and dependence with cognitive function after controlling for confounding variables, a negative effect on social cognition when cannabis is used over time, or negative impacts to reaction time and accuracy when cannabis is used before the onset of psychosis.[4]

Cannabis use may be associated with the development of depressive symptoms.

There is moderate evidence that cannabis use is associated with a small increased risk for the development of depressive disorders. This was primarily based on a meta-analysis that found cannabis use slightly increased the odds for a depressive outcome (OR 1.17: 95% CI: 1.05 to 1.30).[4] The odds were further increased when comparing heavy cannabis users to non-users (OR: 1.62, 95% CI: 1.21 to 2.16).[4] Primary studies reveal mixed findings on the relationship

between cannabis use and depression or depressive symptoms, with confounding variables contributing to the mixed results.[4] The risk for developing depressive symptoms may be increased with early onset, more frequent or intensive use, or the use of potent products.[5] It is unclear whether family history or genetic predisposition influence the relationship between cannabis use and depressive symptoms.[5]

Among individuals with depressive disorders, there is no evidence on whether cannabis use is associated with changes in the course or symptoms of the disorders.[4]

There is uncertainty on the association between cannabis use and the risk of developing bipolar disorder.

There is limited evidence on whether cannabis use is associated with the likelihood of developing bipolar disorder, particularly among regular or daily users.[4]

Among individuals diagnosed with bipolar disorders, there is moderate evidence that regular cannabis use is associated with increased symptoms of mania and hypomania.[4] This is primarily based on a systematic review that found cannabis use may increase the likelihood, severity or duration of manic phases.[4] Primary studies reveal that cannabis use is associated with time to recurrence.[4] Further, weekly and almost daily cannabis use, but not daily cannabis use, was associated with the incidence of mania and hypomania symptoms.[4]

Cannabis use may be associated with suicide.

There is moderate evidence that cannabis use is associated with an increased incidence of suicidal ideation and suicide attempts, with a higher incidence among heavier users.[4] Further, there is moderate evidence of an association between cannabis use and increased incidence of

suicide completion.[4] These conclusions were primarily based on results from two systematic reviews; only one of which was described.[4] The reported systematic review was a meta-analysis that found any cannabis use was associated with an increased odds of suicidal ideation (OR: 1.43, 95% CI: 1.13 to 1.83), suicide attempts (OR: 2.23, 95% CI: 1.24 to 4.00) and death by suicide (OR: 2.56, 95% CI: 1.25 to 5.27).[4] A primary study found that cannabis use at baseline was not associated with an increased risk for developing suicidality at follow-up.[4] The risk for suicide may be increased with earlier onset, or more frequent or intensive use.[5] It is unclear whether family history or genetic predisposition influence the relationship between cannabis use and suicide.[5]

Cannabis use may be associated with social anxiety disorders. There is uncertainty on the association between cannabis use and other anxiety disorders.

There is moderate evidence that regular cannabis use is associated with an increased incidence of social anxiety disorder.[4] There is limited evidence that cannabis use is associated with the development of any other type of anxiety disorder.[4] A meta-analysis found cannabis use at baseline was associated with the development of anxiety symptoms at follow-up after adjusting for confounders such as substance use, psychiatric comorbidity and demographic variables (aOR: 1.28, 95% CI: 1.06 to 1.54).[4] Primary studies found mixed results on the association between cannabis use and anxiety disorders depending on the selection of the exposure variable (i.e., cannabis use or cannabis use disorder), the selection of the outcome variable (i.e., development of anxiety symptoms or incidence of anxiety disorder) and whether adjustments were made for confounding variables.[4] The risk for anxiety disorders may be increased with greater cannabis use frequency.[5] It is unclear whether family history or genetic predisposition influence the relationship between cannabis use and anxiety.[5]

There is limited evidence that near daily cannabis use is associated with increased symptoms of anxiety.[4]

There is uncertainty on the association between cannabis use and posttraumatic stress disorder (PTSD).

There is no evidence regarding whether cannabis use is associated with the development of PTSD.[4]

Among individuals with PTSD, there is limited evidence that cannabis use is associated with an increased severity of PTSD symptoms.[4]

Problem Cannabis Use

Problem cannabis use is more likely when there is an earlier onset of more frequent use.

There is no official distinction between "problem" versus "risky" cannabis use.[4] This contributes to a lack of clarity on the relationship between cannabis use and the progression to use that is considered problematic.[4] Descriptions of cannabis use patterns that precede abuse or dependence remain unclear.[4] Within the National Academies of Sciences, Engineering and Medicine (2017) report, problem cannabis use disorder is defined "various levels of hazardous or potentially harmful cannabis use patterns, including those related to cannabis use disorder, dependence or abuse."[4]

Primary literature results indicate that early cannabis use initiation increases the risk for cannabis dependence,[4,5] with studies finding that the risk is nearly doubled or quadrupled compared to those who initiate use later.[5] On the basis of primary studies, one document

concluded that there is substantial evidence that the initiation of cannabis use at an earlier age increases the risk for developing problem cannabis use.[4]

Primary studies have generally found that more frequent cannabis use (i.e., daily or weekly) increases the risk for developing problem cannabis use (i.e., cannabis dependence, cannabis use disorder).[4,5] On the basis of primary studies, one document concluded that there is substantial evidence that more frequent cannabis use increases the risk of developing problem cannabis use.[4] Further, there is moderate evidence that during adolescence, more frequent cannabis use increases the risk for developing problem cannabis use.[4] A study from the United Kingdom also found that the use of potent products is associated with greater dependence severity, especially among younger users.[5]

Use of Other Substances

Cannabis use may be associated with the development of substance dependence and/or a substance use disorder.

There is moderate evidence that cannabis use is associated with the development of substance dependence and/or a substance use disorder for substances including alcohol, tobacco, and other illicit drugs.[4] This is based on primary studies which have generally found associations between varying histories or levels of cannabis use and problematic alcohol use, tobacco/nicotine dependence, and other substance use problems.[4] The risk of alcohol and illegal drug dependence may be increased with early onset.[5]

There is uncertainty on the association between cannabis use and the initiation of tobacco use or changes in the rates and patterns of other substance use.

There is limited evidence that cannabis use is associated with the initiation of tobacco use as well as changes in the rates and patterns of other licit and illicit substance use.[4] It has been suggested that the risk of other substance use may be increased with early onset or more frequent cannabis use.[5]

Risks with Different Mechanisms for Inhalation

Cannabis inhalation practices may increase the risk for harmful health outcomes.

Certain of modes of cannabis inhalation may increase the potential for health harms:

- The use of practices to intensify the absorption of cannabis' psychoactive properties, such as breath holding or deep inhalation, can increase an individual's exposure to hazardous by-products, such as carcinogens, tar and other toxins, and carbon monoxide.[5]
- The use of bongs or waterpipes can reduce burnt particle inhalation. However, it can increase the intake of tar or particulate matter, and the transmission of infectious disease.[5]
- The use of vaporizers reduces an individual's intake of toxic compounds since cannabis is not combusted.[5] However, there are no rigorous studies on the long-term effects of use. Formaldehyde particles have been detected at higher voltages for cannabis e-cigarettes.[5]
- The inhalation of flash vaporized cannabis concentrates (also known as "dabbing") is associated with an increased risk of hydrocarbon burns and the inhalation of harmful

products, including solder, rust, and benzene.[5] Dabbing is also associated with increased impairment, tolerance, and withdrawal symptoms.[5]

9 Implications for Practice

A facilitated discussion was held with ROP-PH staff to share the findings of this report and identify factors that may influence its application to practice. Participants represented various divisions, including Chronic Disease and Injury Prevention, Family Health, Office of the Medical Officer of Health, and Communications.

Uncertainty and lack of evidence create challenges for developing key messages.

Participants identified potential challenges with using findings that are uncertain, inconclusive, or which provide limited details. For example, the use of the term "earlier initiation" within the evidence was identified as being vague. It was acknowledged that recreational cannabis was legalized before the development of comprehensive evidence base on cannabis-related health effects. Despite the lack of evidence with 'substantial' conclusion statements, the findings were considered a credible and transparent source of information to be used by the organization. ROP-PH should be clear and transparent in communicating where uncertainty exists in the available evidence to accurately inform stakeholders and guide informed decision-making. Some participants suggested conducting a scan of key messages from other organizations to identify types of information being shared and compare potential areas of conflict.

Various internal and external stakeholders are interested in evidence-based key messages on the health effects of recreational cannabis use.

Several community stakeholders were identified as having interest in this topic, including local municipalities, school boards, physicians, children's aid societies, Regional partners such as Human Services, and the general public. Participants stated that some stakeholders may be frustrated with evidence that is uncertain when searching for more definitive answers. Others who've had difficulty finding reputable sources of information will benefit from having access to a credible body of evidence. It was suggested that some stakeholders, such as physicians, may require more detailed information due to differences in using cannabis for medical versus recreational purposes, and their responsibility to counsel patients.

Key messages will need to be tailored to various audiences to ensure clarity and relevance.

Participants identified various factors that may influence how the key messages will be received, including: whether an individual uses cannabis; online literacy and ability to identify trustworthy information; conflicting messaging; and the influence of the cannabis industry. The group discussed the importance of having a common set of messages across the department, with the ability to tailor them as appropriate for different audiences, such as schools or Family Health clients. This will help ensure that stakeholders are receiving relevant, clear, and reliable information.

While the focus of the evidence review was on health effects, multiple participants expressed the importance of incorporating harm reduction messaging when conducting knowledge translation activities. The provision of harm reduction messaging to help lower the risks for

those who use cannabis, as opposed to exclusive abstinence-based methods, is essential given that cannabis use is legal.

It is important to continue monitoring new evidence on recreational cannabis use.

Participants emphasized the need for ongoing monitoring of research evidence, given that recreational cannabis is an evolving body of evidence within a changing legal landscape. ROP-PH must determine an appropriate method of monitoring and updating the evidence and notify applicable stakeholders if there are implications for their practice. Participants suggested connecting with internal committees to expand conversations around the evidence review recommendations. Discussions should also continue regarding the incorporation of harm reduction messaging to provide relevant and credible information to the community.

10 Recommendations

1. Share key messages on the health effects of recreational cannabis use with internal and external stakeholders.
    - Key messages should be tailored to different audiences (e.g., Family Health clients, school board partners).
2. Monitor new research evidence on the health effects of recreational cannabis use on an ongoing basis to determine whether revisions to the key messages are necessary.

11 Acknowledgements

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Shant Alajajian, Librarian Specialist

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Data References

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B. Ontario Student Drug Use and Health Survey, 2017, Centre for Addiction and Mental Health. Region of Peel-Public Health.

Appendices

Appendix A: Search Strategy

Appendix B: Literature Search Flowchart

Appendix C: Data Extraction Tables

Appendix A: Search Strategy

OVID MEDLINE Suite

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 15, 2018>, Global Health <1973 to 2018 Week 32>, Ovid Healthstar <1966 to June 2018>, Ovid MEDLINE(R) <1946 to August Week 2 2018>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <August 20, 2018>, PsycINFO <2002 to August Week 2 2018>

Search Strategy:

1 exp CANNABIS/ (22342)
2 "cannabis".ti,ab. (31264)
3 "marijuana".ti,ab. (27784)
4 "marihuana".ti,ab. (1741)
5 exp CANNABINOIDS/ (22757)
6 "cannabinoid*".ti,ab. (27368)
7 "THC".ti,ab. (9850)
8 "tetrahydrocannabinol*".ti,ab. (9995)
9 exp CANNABIDIOL/ (1776)
10 exp Marijuana Smoking/ (8082)
11 exp Marijuana Abuse/ (10181)
12 "outcome*".ti,ab. (2841126)
13 "effect*".ti,ab. (10212710)
14 "impact*".ti,ab. (1846950)
15 "bene*".ti,ab. (1596243)
16 "risk*".ti,ab. (3937589)
17 "harm*".ti,ab. (305159)
18 exp "Quality of Life"/ (367639)
19 "health*".ti,ab. (4994770)
20 exp Risk Assessment/ (501379)
21 exp RISK/ (1960545)
22 exp Long Term Adverse Effects/ (680)
23 "adverse*".ti,ab. (866590)
24 exp Health Impact Assessment/ (3139)
25 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (89747)
26 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (18554681)
27 ("systematic overview*" or "overview adj review*" or "umbrella review*" or "meta-review*" or "metareview*" or "review adj review" or "guideline*").mp,pt. (823519)
28 25 and 26 and 27 (696)
29 limit 28 to (english language and yr="2013 -Current") [Limit not valid in CDSR; records were retained] (357)
30 remove duplicates from 29 (196)

CINAHL

S20	S16 AND S17 AND S18	**Limiters** - Published Date: 20130101-20181231; English Language; Exclude MEDLINE records **Search modes** - Boolean/Phrase	View Results (28) | Vi
S19	S16 AND S17 AND S18	**Search modes** - Boolean/Phrase	View Results (91) | Vi
S18	"systematic overview*" OR "overview N1 review*" OR "umbrella review*" OR "meta-review*" OR "metareview*" OR "review N1 review*" OR "guideline*"	**Search modes** - Boolean/Phrase	View Results (102,972)
S17	S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15	**Search modes** - Boolean/Phrase	View Results (2,089,043)
S16	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	**Search modes** - Boolean/Phrase	View Results (9,228)
S15	"adverse*"	**Search modes** - Boolean/Phrase	View Results (288,194)
S14	"health*"	**Search modes** - Boolean/Phrase	View Results (1,150,119)
S13	"harm*"	**Search modes** - Boolean/Phrase	View Results (27,955)
S12	"risk*"	**Search modes** - Boolean/Phrase	View Results (468,123)
S11	"bene*"	**Search modes** - Boolean/Phrase	View Results (186,189)
S10	"impact*"	**Search modes** - Boolean/Phrase	View Results (165,422)
S9	"effect*"	**Search modes** - Boolean/Phrase	View Results (756,205)
S8	"outcome*"	**Search modes** - Boolean/Phrase	View Results (449,835)
S7	"cannabidiol*"	**Search modes** - Boolean/Phrase	View Results (138) | V
S6	"tetrahydrocannabinol*"	**Search modes** - Boolean/Phrase	View Results (153) | V
S5	"THC"	**Search modes** - Boolean/Phrase	View Results (306) | V
S4	"cannabinoid*"	**Search modes** - Boolean/Phrase	View Results (982) | V
S3	"marihuana"	**Search modes** - Boolean/Phrase	View Results (51) | Vi
S2	"marijuana"	**Search modes** - Boolean/Phrase	View Results (4,278)
S1	"cannabis"	**Search modes** - Boolean/Phrase	View Results (6,551)

SocINDEX

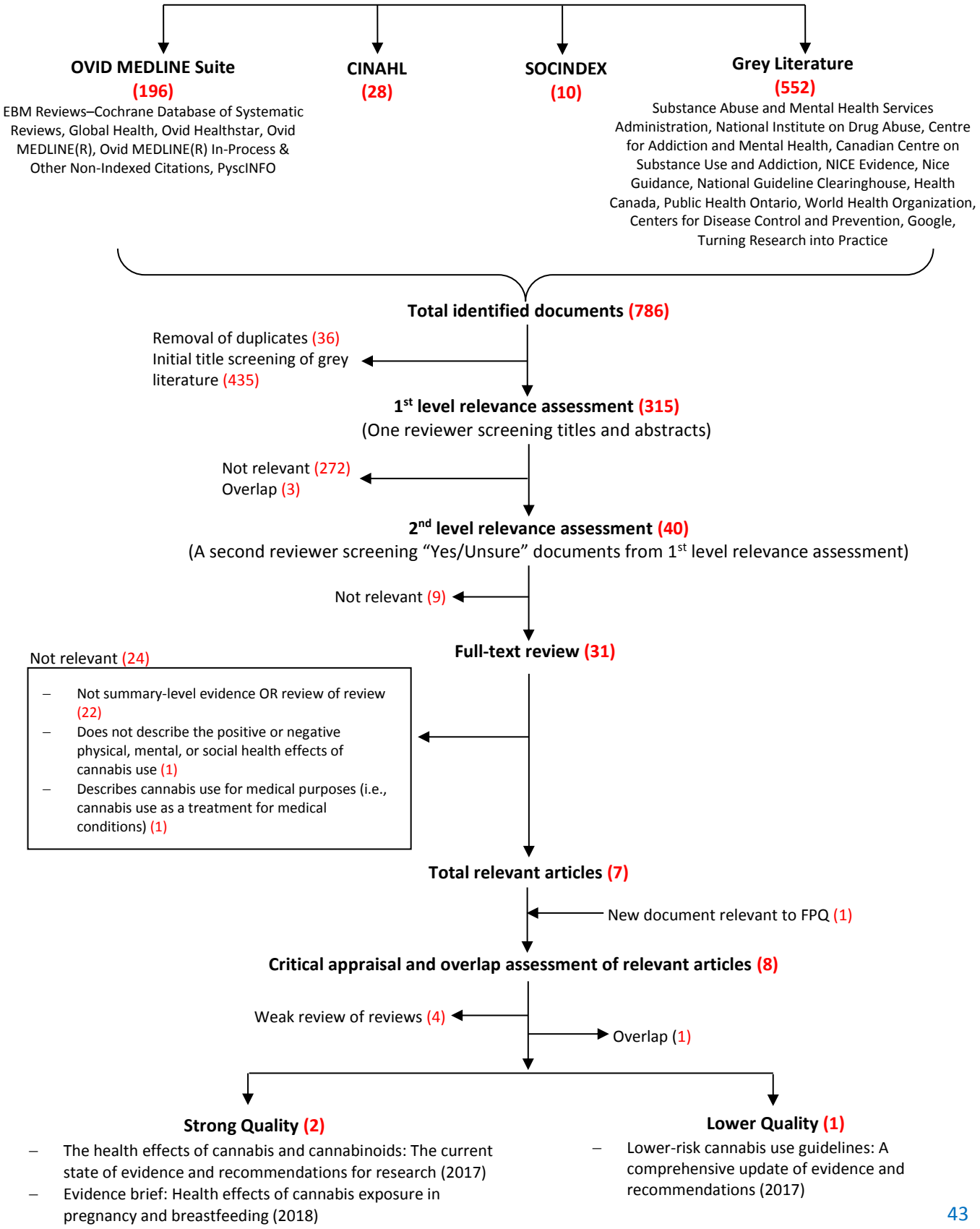
S20	S16 AND S17 AND S18	**Limiters** - Date of Publication: 20130101-20181231 **Search modes** - Boolean/Phrase	View Results (10)
S19	S16 AND S17 AND S18	**Search modes** - Boolean/Phrase	View Results (66)
S18	"systematic overview*" OR "overview N1 review*" OR "umbrella review*" OR "meta-review*" OR "metareview*" OR "review N1 review*" OR "guideline*"	**Search modes** - Boolean/Phrase	View Results (24,034)
S17	S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15	**Search modes** - Boolean/Phrase	View Results (837,914)
S16	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	**Search modes** - Boolean/Phrase	View Results (8,858)
S15	"adverse*"	**Search modes** - Boolean/Phrase	View Results (12,096)
S14	"health*"	**Search modes** - Boolean/Phrase	View Results (374,671)
S13	"harm*"	**Search modes** - Boolean/Phrase	View Results (25,726)
S12	"risk*"	**Search modes** - Boolean/Phrase	View Results (115,027)
S11	"bene*"	**Search modes** - Boolean/Phrase	View Results (91,956)
S10	"impact*"	**Search modes** - Boolean/Phrase	View Results (153,757)
S9	"effect*"	**Search modes** - Boolean/Phrase	View Results (344,513)
S8	"outcome*"	**Search modes** - Boolean/Phrase	View Results (87,194)
S7	"cannabidiol*"	**Search modes** - Boolean/Phrase	View Results (47)
S6	"tetrahydrocannabinol*"	**Search modes** - Boolean/Phrase	View Results (101)
S5	"THC"	**Search modes** - Boolean/Phrase	View Results (235)
S4	"cannabinoid*"	**Search modes** - Boolean/Phrase	View Results (252)
S3	"marihuana"	**Search modes** - Boolean/Phrase	View Results (1,056)
S2	"marijuana"	**Search modes** - Boolean/Phrase	View Results (6,638)
S1	"cannabis"	**Search modes** - Boolean/Phrase	View Results (3,434)

Grey Literature

Website	Search Date	Search Terms	# of Hits	# of Titles Screened	# Carried to 1st Level Relevance Assessment	# Carried to 2nd Level Relevance Assessment	Full-Text Review	# of Relevant Results
SAMHSA	Aug 24, 2018	cannabis OR marijuana	U*	50	8	0	--	--
NIDA	Aug 23, 2018	(cannabis OR marijuana) AND (effect OR impact OR outcome)	270	50	10	0	--	--
CAMH	Aug 23, 2018	(cannabis OR marijuana) AND (effect OR impact)	1,157	50	3	0	--	--
CCSUA	Aug 23, 2018	(cannabis OR marijuana) AND (effect OR impact OR outcome)	223	50	12	2	2	0
NICE Evidence	Aug 22, 2018	(cannabis OR marijuana) AND (effect* OR impact* OR outcome*)	649	50	21	2	2	1
NICE Guidance	Aug 22, 2018	cannabis OR marijuana	16	16	5	1	1	0
NGC	Aug 22, 2018	cannabis OR marijuana	80	50	2	0	--	--
Health Canada	Aug 22, 2018	cannabis OR marijuana	1,111	50	1	0	--	--
PHO	Aug 22, 2018	(cannabis OR marijuana) AND (effect* OR impact* OR outcome*)	31	31	5	1	1	1
WHO	Aug 22, 2018	cannabis OR marijuana	1,040	50	4	1	1	0
CDC	Aug 22, 2018	cannabis OR marijuana	169	50	12	0	--	--
Google	Aug 22, 2018	(cannabis OR marijuana) AND outcome*	25.5 million	50	23	3	3	0
TRIP	Aug 23, 2018	(marijuana OR cannabis) AND (effect* OR impact* OR outcome*)	5,983	50	11	4	4	0
Total				552	117	14	14	2

*U = Undetermined

Appendix B: Literature Search Flowchart



Appendix C: Data Extraction Tables

1. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research (pg. 37)
2. Lower-risk cannabis use guidelines: A comprehensive update of evidence and recommendations (pg. 78)
3. Evidence brief: Health effects of cannabis exposure in pregnancy and breast (pg. 86)

The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research	
General Information and Quality Rating	
Type of Article	Review of reviews
Author(s) and Date	Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda ("the Committee"); Board on Population Health and Public Health Practice; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine (January 2017)
Country	United States of America
Quality Rating	8/10 (Using Health Evidence™ Quality Assessment Tool)
Details of the Review[1]	
Objective(s)	The report has two primary objectives (Note: only the first objective is relevant to the Focused Practice Question (FPQ)): *1.* To review the literature regarding the health consequences of using cannabis or its constituents • To make recommendations for a research agenda that identifies the most critical research questions to answer regarding the health outcomes related to cannabis use
Databases Searched	2. Medline, Embase, Cochrane Database of Systematic Reviews, PsycINFO
Search Period	3. January 1999 to August 2016
Inclusion/Exclusion Criteria	Inclusion criteria: • English language (1-5) • Article must be related to one of the health topics and specific health endpoints identified by the Committee (Note: this was not explicitly described) Exclusion criteria: 4. For primary literature, excluded "editorials, opinion pieces, grey literature, and other documents that were not peer-reviewed cross-sectional studies, case-control studies, cohort studies, randomized controlled trials, or non-systematic literature reviews" (B-5)

[1] The reported outlined a general methodology. However, any deviations from the general approach are noted within the chapters.

Article Prioritization During Relevance Screening	• The Committee adopted a process for prioritizing evidence:
	  ○ For health endpoints with more than 1 good- or fair-quality systematic review, the Committee prioritized the most recently published systematic review starting from 2011.
	  ○ For endpoints with an associated good- or fair-quality systematic review, the Committee also reviewed relevant primary literature published after the date limits used of the systematic review.
	  ○ "For endpoints not addressed by at least one good- or fair- quality systematic review, the Committee reviewed all relevant primary literature published between January 1, 1999 and August 2, 2016" (B-5)

Number and Type(s) of Articles Included	5. Systematic reviews and primary literature (Note: The types of included primary literature are not summarized. The Inclusion/Exclusion Criteria subsection provides an indication of the types of articles that are included)
	6. The number of articles per health topic was provided, but not for the overall report (Note: Only topics #1-6 are relevant to the FPQ, with some duplication in articles across topics):
	  1. **Injury and death:** 18 (2 systematic reviews, 16 primary literature)
	  2. **Cancer and immunity/infection:** 29 (3 systematic reviews, 26 primary literature)
	  3. **Psychosocial:** 21 (5 systematic reviews, 16 primary literature)
	  4. **Mental health:** 8 (15 systematic reviews, 72 primary literature)
	  5. **Pregnancy:** 34 (1 systematic reviews, 33 primary literature)
	  6. **Cardiovascular and respiratory:** 24 (1 systematic reviews, 23 primary literature)
	  7. **Therapeutic:** 38 (17 systematic reviews, 21 primary literature)

Quality Appraisal Process and Results	• Separate quality assessment processes were used for different types of articles:
	  ○ Systematic reviews were based on 5 attributes adapted from other sources by at least 2 reviewers: study eligibility criteria, identification and collection of studies, data collection and study appraisal, synthesis and findings, conflict of interest
	  ○ Primary literature were assessed using Cochrane Quality Assessment and Newcastle-Ontario scale. The number of reviewers were not specified.
	• Quality assessment scores for each included article were not provided. However, only good- or fair-quality systematic reviews and primary research literature were used.

Strength of Evidence Assessment	• The Committee developed a set of categories to describe the strength of the evidence informing each conclusion. These categories do not reflect the magnitude of effect or level of importance, but rather the quality, quantity and consistency of evidence supporting a conclusion. Private deliberations within committee subgroups were held.
	• Weight-of-Evidence Categories are listed below (Note: only the details relevant to non-therapeutic health effects are described):
	a) Conclusive Evidence
	  – Strong evidence from RCTs to support or refute a statistical association
	  – "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" (S-5)
	b) **Substantial Evidence**

<table>
<tr><td></td><td>
– Strong evidence to support or refute a statistical association
– “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” (S-5,6)
c) Moderate Evidence
– Some evidence to support or refute a statistical association
– “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” (S-6)
d) Limited Evidence
– Weak evidence to support or refute a statistical association
– “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” (S-6)
e) No or Insufficient Evidence to Support the Association
– No or insufficient evidence to support or refute a statistical association.
– “For this level of evidence, there are mixed, a single poor study, or health endpoint has not been studied at all. No conclusions can be made because of substantial uncertainty due to chance, bias, and confounding factors.” (S-6)
</td></tr>
<tr><td colspan="2">Characteristics of the Review</td></tr>
<tr><td>Study Population(s)</td><td>
• Not focused on one specific population; although certain chapters focused on specific groups (e.g., pregnant women, offspring, populations experiencing mental health disorders)
• “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” (S-2)
</td></tr>
<tr><td>Exposure(s)</td><td>
• Cannabis use (Note: most of the evidence reviewed is based on epidemiological research primarily focused on smoked cannabis)
</td></tr>
<tr><td>Outcome(s)</td><td>
• The report includes the following health topics and endpoints related to therapeutic and non-therapeutic use (Note: Only the health topics and endpoints related to non-therapeutic use are relevant to the FPQ):
<table>
<tr><th>Health Topic</th><th>Health Endpoint</th></tr>
<tr><td>Therapeutic effects</td><td>Chronic pain; cancer, chemotherapy-induced nausea/vomiting; appetite and weight loss; irritable bowel syndrome; epilepsy; spasticity related to multiple sclerosis; Tourette syndrome; amyotrophic lateral sclerosis; Huntington’s disease; Parkinson’s disease; dystonia; Alzheimer’s disease/dementia; glaucoma; traumatic brain injury/spinal cord injury; addiction; anxiety; depression; sleep disorders; posttraumatic stress disorder; schizophrenia</td></tr>
</table>
</td></tr>
</table>

	Cancer	Lung cancer; oral cancer; esophageal cancer; testicular cancer; other cancer
	Cardiometabolic risk	Acute myocardial infarction; stroke; metabolic dysregulation; metabolic syndrome, prediabetes, and diabetes
	Respiratory disease	Pulmonary function; respiratory symptoms (including chronic bronchitis); chronic obstructive pulmonary disorder; asthma
	Immunity	Immune function; infectious disease
	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/income; social relationships and other social roles
	Mental health	Schizophrenia and other psychotic disorders; 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

- (Note: "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, and the population studied' (S-4)

Results of the Review	

Relevant Review Results[2]	**Cancer (Ch. 5)**
	Chapter Conclusions:
	• There is **moderate evidence** of no statistical association between cannabis use and:
	  ○ Incidence of lung cancer (cannabis smoking)
	  ○ Incidence of head and neck cancers
	• There is **limited evidence** of a statistical association between cannabis smoking and:
	  ○ Non-seminoma-type testicular germ cell tumours (current, frequent, or chronic cannabis smoking)
	• There is **insufficient evidence** to support or refute a statistical association between cannabis use
	  ○ Incidence of esophageal cancer (cannabis smoking)
	  ○ Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal

[2] Only the number and types of studies were reported for chapter conclusions labelled with "limited" or "no/insufficient" evidence.

cancer, Kaposi's sarcoma, or bladder cancer
    - Subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use)

Additional Chapter Notes:

- Epidemiological studies that investigate the association between cannabis use and the risk of various cancers risks face methodological challenges, including:
    - Small sample sizes and low participation rates
    - The inability to verify cannabis use data based on self-report alone
    - Difficulties in controlling for potential confounders and accounting for potential effect modifiers" (5-13)
- There are unique challenges pertaining to cancer studies:
    - Some risk factors (e.g., family cancer history, occupational exposures, diet) are difficult to measure.
    - The long incubation period of many cancers requires makes it difficult to fully characterize the relevant cannabis exposure and to control for other relevant exposures (5-13)

Lung Cancer

- This subsection is based on 1 systematic review, and 1 non-systematic epidemiologic review

Systematic Review

- A systematic review/meta-analysis evaluated the impact of key characteristics of cannabis smoking on lung cancer incidence.
    - They examined this "among all study participants as well as a sub-group who were not tobacco smokers." (5-1)
    - Authors "pooled data on 2,159 lung cancer cases and 2,985 controls from 6 case-control studies" (5-1)
    - The review found "among all study participants, there was no statistically significant difference in the risk of lung cancer for habitual cannabis smokers as compared to non-habitual smokers (Odds Ratio (OR) 0.96, 95% Confidence Interval (CI)=0.66 to 1.38)" (5-1)
    - Among participants who did not smoke tobacco, the risk of lung cancer was not significantly higher or lower for habitual cannabis smokers than for non-habitual cannabis smokers (OR 1.03, 95% CI=0.51 to 2.08) (5-2)
    - The study authors noted the following limitations:
        - Potential effect measure modifiers (e.g., variations in smoking technique, characteristics of cannabis smoked) could not be accounted for in the study
        - The small number of participants who were heavy and chronic users made effect estimates for these subgroups imprecise
        - The study relied on self-reports without biological validation of use patterns

Primary Literature

- An epidemiologic review was conducted to assess the association between cannabis use and the incidence of several

cancers, including lung cancer

- The review evaluated 6 studies on cancer, including the systematic review described above, as well as 2 studies within that review
- Excluding the 3 studies that overlapped with the systematic review described above, the 3 remaining studies indicate an increased risk for lung cancer associated with smoking cannabis (data only provided for 1 of the 3 remaining studies)

Head and Neck Cancers

- This subsection is based on 1 systematic review. Good-quality primary literature published after the most recently published good- or fair-quality systematic review was not identified.

Systematic Review

- The systematic review/meta-analysis evaluated "the association between cannabis use and the incidence of head and neck cancers, including upper aerodigestive tract, oral cavity, and nasopharyngeal cancers, as well as on head and neck squamous cell carcinoma" (5-3)
  - The review/meta-analysis included 9 case-control studies from 6 articles, totalling 13,931 participants
  - "The meta-analysis found no significant association between cannabis use and head and neck cancers (OR 1.021, 95% CI=0.912 to 1.143)" (5-3). The authors adjusted for tobacco use, age, gender and race
  - Review authors concluded that "there was 'insufficient epidemiological evidence to support a positive or negative association of marijuana use and the development of [head and neck cancers]'" (5-3)
  - The review authors noted the following limitations:
    - "Although a non-significant association was observed for head and neck cancers as a group, this finding does not preclude the existence of a significant positive or negative association between cannabis use and the incidence of specific types of head and neck cancer
    - The systematic review also relied on cohort studies, which may not detect less pronounced risks or risks that emerge over longer periods
    - Differences in the methods employed in these studies prevented an analysis of how the characteristics of cannabis use affect the risk of head and neck cancers" (5-3)

Testicular Cancer

- This subsection is based on 1 systematic review/meta-analysis and 1 non-systematic epidemiologic review/meta-analysis.

Esophageal Cancers

- This subsection is based on 1 case-control study. A good- or fair-quality systemic review was not identified.

Other Cancers in Adults

- Cancers discussed in this subsection include: prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin

lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, bladder cancer
- This subsection is based 1 non-systematic epidemiologic review and 1 other primary literature article where the design was not stated. No systematic reviews were identified.

Parental Cannabis Use and Cancer in Offspring

- Cancers discussed in this subsection include: acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, neuroblastoma
- This subsection is based 1 non-systematic epidemiologic review. A good- or fair-quality systemic review was not identified.

Cardiometabolic Risk (Ch. 6)

Chapter Conclusions:

- "There is **limited evidence** of a statistical association between cannabis use and:
  - The triggering of acute myocardial infarction (cannabis smoking)
  - Ischemic stroke or subarachnoid hemorrhage
  - Decreased risk of metabolic syndrome and diabetes
  - Increased risk of prediabetes
- 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." (6-12)

Additional Chapter Notes:

- Limitations of the reviewed studies include:
  - "Lack of information on different routes of cannabis administration (e.g., smoked, edible, etc.)
  - Lack of adequate dose information
  - Insufficient information on potential additives or contaminants
  - Inadequate data on total lifetime duration/dose of cannabis use" (6-12)

Acute myocardial infarction

- This subsection is based on 1 retrospective cohort study and 1 case crossover study. A good- or fair-quality systematic review was not identified.
- Three descriptive review articles provided useful background for the Committee.

Ischemic stroke or subarachnoid hemorrhage

- This subsection is based on 3 cross-sectional studies, 1 case-control study, and 1 retrospective cohort study. A good- or fair-quality systematic review was not identified.

Metabolic dysregulation, metabolic syndrome, prediabetes or diabetes mellitus

- This subsection is broken down into 3 topics and informed by the following studies (Note: No good- or fair-quality systematic reviews were identified for any of the 3 topics):
  - Metabolic dysregulation and metabolic syndrome (3 cross-sectional studies)
  - Prediabetes (1 study where the design was not clearly specified)
  - Diabetes (2 cross-sectional studies, 1 study where the design was not clearly specified)
- A review published after the literature search period informed the discussion in this subsection.

Respiratory Disease (Ch. 7)

Chapter Conclusions:

- "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)
- There is **moderate evidence** of a statistical association between cannabis smoking and:
  - Improved airway dynamics with acute use, but not with chronic use
  - Higher forced vital capacity
- There is **moderate evidence** of a statistical association between the cessation of cannabis smoking and:
  - Improvements in respiratory symptoms
- 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)" (7-12)
- "There is **insufficient evidence** to support or refute a statistical association between cannabis smoking and:
  - Hospital admission for COPD" (7-7)
- "There is **no or insufficient evidence** to support or refute a statistical association between cannabis smoking and:
  - Asthma development or asthma exacerbation" (7-11)

Additional Chapter Notes:

- Limitations of reviewed studies include:
  - Difficulties in separating the effects of cannabis smoking from tobacco smoking in currently available data
  - Use of self-report to assess cannabis smoking
  - The lack of cohort studies of regular or daily cannabis users, adequate controls for environmental factors and generalizability of findings

Respiratory symptoms (including chronic bronchitis)

- "Respiratory symptoms include cough, phlegm, and wheeze. Chronic bronchitis is defined as chronic phlegm production or productive cough for 3 consecutive months per year for at least 2 consecutive years" (7-7)

- This subsection is based on 1 systematic review, 2 cross-sectional studies, 1 cohort study, 1 longitudinal study, 1 feasibility study

Systematic review:

- The systematic review examined the association between long-term cannabis smoking and respiratory symptoms in 14 studies (9 cross-sectional, 3 case-series, 1 case-control, 1 longitudinal cohort)
    - "Data were relatively consistent in both cross-sectional and cohort studies in indicating that long-term cannabis smoking worsens respiratory symptoms including:
        - Cough (OR 1.7-2.0)
        - Increased sputum production (OR 1.5-1.9)
        - Wheeze (OR 2.0-3.0)
    - Other studies have reported effects on more episodes of acute bronchitis and pharyngitis, dyspnea, hoarse voice, worse cystic fibrosis symptoms, chest tightness" (7-8)

Primary Studies:

- A cross-sectional study found that compared to non-smokers, cannabis smokers reported a higher prevalence of wheeze, cough, chest tightness, and chronic bronchitis symptoms.
    - "There was no clear additive effects observed in the combined cannabis and tobacco smoking groups on respiratory symptoms" (7-8)
- A cross-sectional study found that frequency of use, the amount used, and the degree of usual intoxication were all positively associated with more respiratory symptoms.
- A cohort study assessed previous-year cannabis and tobacco smoking (at 5 time points) and found that:
    - Frequent cannabis use (using marijuana ≥52 times over the previous year) was not associated with dyspnea ($p=0.09$), but associated with:
        - Morning cough (OR 1.97, $p<0.001$)
        - Sputum production (OR 2.31, $p<0.001$)
        - Wheeze (OR 1.55, $p<0.001$)
    - Quitters (defined as a frequent cannabis user at the previous assessment but less frequent at the current assessment) had fewer respiratory symptoms than those who did not quit.
- A longitudinal study examined the relationship between symptoms for chronic bronchitis and cannabis use in 299 participants over 9.8 years (for at least 2 visits).
    - Authors found that compared to never users, current cannabis users were more likely to have:
        - Cough (OR 1.7, no CIs provided)
        - Sputum (OR 2.1, no CIs provided)
        - Increased bronchitis episodes (OR 2.3, no CIs provided)
        - Wheeze (OR 3.4, no CIs provided)
    - Authors found that compared to former users, current cannabis users were more likely to have:

- Cough (OR 3.3, no CIs provided)
- Sputum (OR 4.2, no CIs provided)
- Wheeze (2.1, no CIs provided)

- A feasibility study (no control group) of 12 adult participants "who did not develop a respiratory illness during the trial found that the use of a cannabis vaporizer instead of smoking cannabis was correlated with the resolution of cannabis-related respiratory symptoms at approximately 1 month after the introduction of the vaporizer". (7-9)

Additional Sub-Chapter Notes

- General limitations of the literature include:
  - The failure to control for tobacco, occupational, and other environmental exposures
  - The failure to control for the dose or duration of cannabis smoke or exposure
  - Basing heavy cannabis exposure on exceeding a specific threshold of cigarettes instead of using joint-years (Even among studies using joint-years, there is still a lack of clarity on the generalizability of findings "given the potential high variability in THC content from joint to joint and from year to year." (7-9))

Pulmonary function (airway dynamics and vital capacity)[3]

- "Pulmonary function refers to lung size and function" (7-2)
- This subsection is based on 1 systematic review, 2 cross-sectional studies, 1 longitudinal study, 1 cohort study, and 1 feasibility study

Systematic Review

- A systematic review examined the relationship between cannabis smoking and airway response as well pulmonary function in 34 publications (12 focused on airway response, 14 reported on pulmonary function)
  - Short-term exposure to cannabis smoking was found to result in bronchodilation
    - "Specifically, acute cannabis smoking was consistently associated with improvements in specific airway conductance, peak flow measurements, and forced expiratory volume in 1 (FEV_1) second and reversed bronchospasm from challenges by either methacholine or exercise." (7-2)
  - "Any short-term benefits, however, were offset by effects of long-term cannabis smoking." (7-2)
    - Regular smoking was associated with lower specific airway conductance on average by 16%, as well as a lower FEV_1.
    - "There was also a dose-response effect between average daily quantity of cannabis and a lower specific airway conductance.
    - However, the clinical significance of the association between regular cannabis smoking and a lower specific airways conductance is not known." (7-2)

[3] Information related to pulmonary function were determined to be clinically focused. This information was extracted but not incorporated into FPQ synthesis.

- "Other studies that examined the association between long-term cannabis smoke exposure and pulmonary function have inconsistently found lower or no change in FEV_1, FVC, FEV_1/FVC, diffusing capacity for carbon monoxide (DLCO), and airway hyper-responsiveness" (7-2)

Primary Studies

- A cross sectional study did not find an association between long-term cannabis smoking and pulmonary function variables.
  - However, when cannabis smoking was analyzed in terms of joint-years, there was "a significantly lower FEV_1/FVC, lower specific airways conductance, and a higher total lung capacity per joint-year smoked in cannabis smokers compared to non-smokers" (7-3)
  - "The authors estimated that the negative association between each cannabis joint and a lower FEV_1/FVC was similar to that of 2.5 to 5 tobacco cigarettes." (7-3)
- A cross-sectional study examined survey data on 10,327 adults
  - The authors "found that current smokers had a smaller FEV_1/FVC than never smokers (-0.01 and -0.02, respectively), and they observed moderate to large increases in FEV_1 (49 mL and 89 mL, respectively) and FVC (159 mL and 204 mL, respectively) when comparing current smokers to never smokers." (7-3)
  - Authors also found "an important decrease in exhaled nitric oxide among current smokers when compared to never smokers (-7 per cent versus -14 per cent) but it is unclear if this effect was confounded by the high prevalence of tobacco smoking in current cannabis users" (7-3)
- A longitudinal study analyzed data on 5,115 adults
  - The authors found that "occasional and low cumulative cannabis smoking was not associated with adverse effects on pulmonary function" (7-3)
  - "There was a trend toward decreases in FEV_1 over 20 years only in the heaviest cannabis smokers (≥20 joint-years)."
  - There was a "higher-than-expected FVC among all categories of smoking intensity" (7-3)
- A cohort study examined cannabis and tobacco use in participants from childhood to adulthood
  - Cumulative cannabis use (quantified as joint-years since age 17 years) was associated with higher FVC, total lung capacity, functional residual capacity and residual volume, but not with lower FEV_1 or FEV_1/FVC
- A feasibility study "found that the use of cannabis vaporizer instead of smoking cannabis in 12 adult participants who did not develop a respiratory illness was associated with improvements in forced expiratory volumes at approximately 1 month after the introduction of the vaporizer" (7-3)

Additional Sub-Chapter Notes

- Overall, acute cannabis smoking was associated with bronchodilation, but many of the authors agreed that any benefits may be offset when cannabis is smoked regularly. The current findings are inconclusive on a variety of pulmonary function measurements.
- General limitations of the primary studies include:

- Failure to control for tobacco smoking, occupational/other environmental exposures, dose or duration of cannabis smoking
- Basing heavy cannabis exposure on exceeding a specific threshold of joints instead of using joint-years (Even among studies using joint-years, there is still a lack of clarity on the generalizability of findings "given the potential high variability in lung-toxic content from joint to joint." (7-4))

- The Committee noted that "neither the mechanism nor the clinical significance of the association between cannabis smoking and pulmonary function deficits is known, beyond the possible impact of a high FVC in lower the FEV_1/FVC ratio. While elevated lung volumes could be indicators of lung pathology, an elevated FVC by itself has not been associated with lung pathology" (7-4)

Chronic Obstructive Pulmonary Disease (COPD)

- This subsection is based on 3 cross-sectional studies and 2 studies where the design was not clearly specified. A good- or fair-quality systematic review was not identified.

Asthma

- This subsection is based on 1 systematic review and 2 cohort studies

Immunity (Ch. 8)

Chapter Conclusions:

- "There is **limited evidence** of a statistical association between cannabis smoking and:
  - A decrease in the production of several inflammatory cytokines in healthy individuals
- There is **limited evidence** of no statistical association between cannabis use:
  - The progression of liver fibrosis or hepatic disease in individuals with viral Hepatitis C (HCV) (daily cannabis use)" (8-11)
- There is **insufficient evidence** to support or refute a statistical association between cannabis use and:
  - "Other adverse immune cell responses in healthy individuals (cannabis smoking)" (8-4)
  - "Adverse effects on immune status in individuals with HIV (cannabis or dronabinol use)" (8-6)
  - "Increased incidence of oral human papilloma virus (HPV) (regular cannabis use)" (8-9)

Additional Chapter Notes:

- Most of the scientific literature is comprised of "animal- and cell-based immunological approaches to show that cannabinoids modulate (either suppressing or enhancing) the functions of most of the type of immune cells that have been evaluated." (8-1) Investigations on human immunity are limited.
- "Many of the studies in which the effects of cannabis on the immune system were evaluated possess significant shortcoming in experimental design" (8-11), such as
  - Small numbers of study participants

- Insufficiency in determining adverse effects
- A narrow scope of immunological assessments
- Limited information concerning the levels of cannabis exposure

Immune competence in individuals without an infectious disease (production of inflammatory cytokines and adverse immune cell response)

- This subsection is based on 2 longitudinal studies and 3 studies where the design was not clearly specified. A good- or fair-quality systematic review was not identified.

Immune status of individuals infected with viral hepatitis C

- This subsection is based on 1 prospective study and 2 studies where the design was not clearly specified. A good- or fair-quality systematic review was not identified.

Immune status in individuals with HIV

- This subsection is based on 1 prospective RCT, 1 longitudinal study, and 1 study where the design was not clearly specified. A good- or fair-quality systematic review was not identified.

Susceptibility to Oral Human Papilloma Virus (HPV)

- This subsection is based on 2 cross-sectional studies. A good- or fair-quality systematic review was not identified.

Aspergillus Infection[4]

- Note: No chapter conclusion was provided for this outcome.
- This subsection describes results from case series, case reports, and 1 case-control study.
- "Cannabis has been demonstrated to harbor *Aspergillus* spores, and case reports suggest cannabis use may be associated with aspergillosis in immunocompromised patients"

Injury and Death (Ch. 9)

Chapter Conclusions:

- "There is **substantial evidence** of a statistical association between cannabis use and:
  - Increased risk of motor vehicle crashes
- 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" (9-17)

[4] As there was no chapter conclusion related to aspergillus infection, information was not extracted or incorporated into the FPQ synthesis.

- There is **insufficient evidence** to support or refute a statistical association between cannabis use and:
  - All-cause mortality (self-reported cannabis use)
  - Occupational accidents or injuries (general, non-medical cannabis use)
  - Death due to cannabis overdose

Motor vehicle crashes (MVC)

- The Committee identified 6 fair- or good-quality systematic reviews, but only described the most comprehensive and recently published review. Good-quality primary literature published after the most recently published good- or fair-quality systematic review was not identified.

Systematic Review

- The prioritized systematic review summarized the association between driving under the influence of cannabis and MVCs from 21 case-control or culpability studies
  - Driving under the influence of cannabis (as indicated by self-reported cannabis use or presence of THC metabolite in biological measures) was associated with 20-30% higher odds of an MVC
  - The specific ORs were "1.36 (95% CI=1.15 to 1.61) for an analysis using a random-effects approach and 1.22 (95% CI=1.10 to 1.36) for a meta-regression analysis using a precision-effect estimate with standard errors (PEESE) technique" (9-10)
    - "Sub-group analyses that accounted for alcohol intoxication found the magnitude of ORs weakened to 1.11 (95% CI=1.04 to 1.18) when using random-effects and to 1.18 (95% CI=1.07 to 1.30) when using PEESE" (9-10)
    - "An analysis that did not account for alcohol intoxication found that the ORs were 1.79 (95% CI=1.28 to 2.51) and 1.69 (95% CI=1.25 to 2.28)" (9-10)
  - Limitations of the systematic review:
    - "DUIC may not have just referred to acute intoxication." (9-10) Individuals who reported recent or regular cannabis use but who were neither intoxicated nor impaired while driving may have been considered as DUIC. Additionally, the association between blood THC levels and acute intoxication/driving impairment is not clear
    - Different methods were used to assess cases and controls in 3 out of 21 studies which may lead to a non-differential misclassification of exposure
    - The review does not determine the dose at which driving becomes sufficiently unsafe as to increase MVC risk
    - Cohort studies were not included in the systematic review
  - Strengths of the systematic review/meta-analysis:
    - The authors included a wide range of recent studies, including non-peer-reviewed data
    - It adjusted for potential confounders, including alcohol

Overdose injuries and death

- A good- or fair-quality systematic review was not identified.
    - For overdose injuries, case series were described but they did not inform the committee's conclusions on the association between cannabis use and overdose injuries. Therefore, this information is not captured below. Primary literature were described and included 1 retrospective review of records and 4 studies where the designs were not clearly specified
    - For overdose deaths, a few studies and case reports were described but they did not inform the Committee's conclusions on the associations between cannabis use and death. Therefore, this information is not captured below.

Primary Literature

- Overdose injuries
    - A retrospective review examined cases of unintentional cannabis ingestions among children who required medical attention at a Colorado children's hospital
        - "Out of 1,378 unintentional ingestions, only 14 were cannabis-related, of which 13 were observed in the ER or admitted to the hospital" (9-13)
        - "Symptoms included lethargy, ataxia, dizziness, and respiratory insufficiency" (9-13)
        - The proportion of cannabis-related unintentional ingestions significantly increased from 0% in 2005-2009 to 2.4% in 2009-2013; coinciding with the U.S. Department of Justice's decision in 2009 to no longer prosecute cannabis users and suppliers who adhere to state laws.
    - A study reported the prevalence of unintentional pediatric cannabis exposures occurring between 2009 and 2015 at a Colorado poison centre and children's hospital
        - Between 2012/13 to 2014/15, the average number of cannabis-related calls per 1,000 calls to the poison center increased significantly from 0.9 to 2.3.
            - These periods correspond to the two years before and after legalization of recreational cannabis in Colorado (9-13)
            - "Symptoms reported in the 163 calls received by the poison center included drowsiness and/or lethargy (49% of cases), ataxia and/or dizziness (12%), and agitation (8%)" (9-13)
        - Between 2012/13 to 2014/15, the average number of cannabis-related emergency department visits per 1,000 visits increased from 4.3 to 6.4, though non-significantly (9-13)
            - "Out of 81 cases received by the children's hospital, 40% were observed in the emergency department, 22 were admitted to an inpatient ward or the intensive care unit, and 2 required respiratory support" (9-13)
        - "The mean number of calls to poison control centers for unintentional pediatric cannabis exposures increased by 34% per year between 2009 and 2015- a significant increase that was also significantly greater than the 19% annual increase in cannabis-related calls received by poison control centers throughout the rest of the United States during the same period" (9-14)

	○ A study reviewed data from the National Poison Data System between 2000 and 2013 ▪ During this period, U.S. poison centers received 1,969 calls related to cannabis exposure among children younger than 6 years old (9-13) ▪ Most exposures were unintentional (92.2%) and resulted from ingesting cannabis or a cannabis product (75.0%) ▪ "Drowsiness and/or lethargy accounted for nearly half of report clinical symptoms (45.5%), while more serious effects, including coma (0.9%), cardiovascular symptoms (4.1%), and respiratory depression (0.7%), occurred less frequently." (9-13) ▪ "The annual rate of exposures increased over time, from a national average of 4.21 per million children in 2006 to 10.42 per million children in 2013, corresponding to a statistically significant increase of 147.5%." (9-13) ▪ Between 2006 and 2013, "the increase in the annual rate of exposures among states that had legalized medical cannabis prior to 2000 was significant, at 609.6%" (9-13) ▪ "Between 2000 and 2013, the annual rate of poison control center calls related to cannabis exposures among children younger than 6 was 2.82 times higher in states that had legalized medical cannabis prior to 2000 than in states where medical cannabis remained illegal as of 2013" (9-14) ○ A study examined rates of calls to poison control centers for unintentional pediatric cannabis exposures ▪ The study found that "between 2005 and 2011, the rate of calls to poison centres: • Did not increase in states where cannabis remained illegal as of 2012 • Increased by 11.5% (95% CI= -0.4% to 24.7%) in states where legislation to legalize cannabis was passed between 2005 and 2011 • Increase by 30.3% (95% CI=22.5% to 38.5%) in states where cannabis was legalized before 2005" (9-14) ▪ "Among children unintentionally exposed to cannabis, those living in states where cannabis was legalized before 2005 [were] more likely to: • Be evaluated in a health care facility (OR 1.9, 95% CI=1.5 to 2.6) • Experience major or moderate effects (OR 2.1, 95% CI=1.4 to 3.1) • Be admitted to critical care units (OR 3.4, 95% CI=1.8 to 6.5) as compared to those living in states where cannabis remained illegal as of 2013" (9-14) ▪ Ingestion was the most common route of unintentional pediatric exposure (78% of all incidents) ○ The Colorado Department of Public Health and Environment found "moderate evidence that more unintentional pediatric cannabis exposures have occurred in states with increased legal access to cannabis and that the exposures can lead to significant clinical effects requiring medical attention" (9-14) ○ "Most study limitations were related to origin, quality, and completeness of data" (9-14) ○ "Findings based on data from a single children's hospital or regional poison centers may not be generalizable to other facilities or poison centers, especially those in areas where laws regarding cannabis use are different than in Colorado." (9-15)

Additional Sub-Chapter Notes

- Additional study limitations:
  - "Search strategies employed in retrospective reviews of records from hospitals and poison centers may fail to capture all pertinent records, and some records may be incomplete" (9-15)
  - "Data from poison centers will capture only the subset of cannabis-related overdose injuries or deaths that resulted in a call to a poison center and may overrepresent serious cases or cases from states where cannabis is legal" (9-15)
  - "Cannabis exposures are not identical to poisonings and overdoses; consequently, data on trends in cannabis exposures does not necessarily allow for an estimation of trends in cannabis overdose or poisoning" (9-15)

All-cause mortality

- This subsection is based on 1 systematic review and 2 studies where the design was not clearly specified.

Occupational Injury

- This subsection is based on 1 non-systematic literature review, 1 longitudinal study, 1 cross-sectional study, and 2 studies where the design was not clearly specified. A good- or fair-quality systematic review was not identified.
- Articles published prior to 1999 or with closely related research questions oriented the Committee to the broader literature on risk factors for occupational injury but did not directly inform the committee's conclusions.

Prenatal, Perinatal, and Neonatal Exposure to Cannabis (Ch. 10)

Chapter Conclusions:

- "There is **substantial evidence** of a statistical association between maternal cannabis smoking and:
  - Lower birth weight of the offspring
- There is **limited evidence** of a statistical association between maternal cannabis smoking and:
  - Pregnancy complications for the mother
  - Admission of the infant to the neonatal intensive care unit
- 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)" (10-14)

Additional Chapter Notes:

- Limitations of studies in this chapter:
  - Almost exclusive reliance on self-report to determine cannabis exposure; lack of biological validation of self-report
  - The number of women who used cannabis in included studies was small. This may have limited statistical power to detect any outcomes

- Cannabis exposure was almost always through smoking and confounded by use of other substances, namely tobacco and alcohol. “Even when cannabis is the sole exposure, it is not straightforward to attribute outcomes to THC alone versus the mode of exposure”
- “Caution needs to be used in interpreting the numerous findings of “no association” in this chapter. Absent a pooled estimate of effect and confidence intervals, such conclusions may be based on a small number of studies, some of which may even conflict” (10-13)

Fetal growth and development

- This subsection is broken down into the following 5 topics and informed by the following studies:
  - Birthweight (1 systematic review, 3 studies where the designs were not clearly specified)
  - Birth length (1 systematic review, 2 studies where the designs were not clearly specified)
  - Head circumference (1 systematic review, good-quality primary literature published after the most recently published good- or fair-quality systematic review was not identified)
  - Intrauterine growth restriction/Small for gestational age (1 systematic review, 2 studies where the designs were not clearly specified)
  - Congenital malformation (1 systematic review, 2 case-control studies, 2 studies where the designs were not clearly specified)

  (Note: Only the birthweight topic received a chapter conclusion rated as “substantial”)

- <u>Birthweight</u>

  Systematic review

  - The systematic review included studies that examined the effect of cannabis exposure on birth weight; specifically mean birth weights and the percentage of infants at low birth weight (defined as 2.2kg or 5.5 lbs) (10-4)
    - In utero exposure to cannabis is associated with a decrease in birth weight among cannabis exposure infants (pOR 1.77, 95% CI=1.04 to 3.01; pMD -109.42, 95% CI= -38.72 to -180.12)

  Primary Literature

  - Two studies found lower mean birthweights for infants prenatally exposed to cannabis than infants who were not.
    - One study found a -84.20g difference (95% CI= -174.7 to -6.4; p=0.005) in birthweight for the children of mothers who had used cannabis at least once per week before and throughout pregnancy versus non-users.
    - One study found that when looking solely at cannabis using mothers (independent from tobacco use), there was a mean birth weight of 3,161g (SD 689; P=0.051) among infants who had been exposed to cannabis, and 3,417g (SD 504; p=0.051) among infant who had not been

- One study found that after adjusting for drug use (i.e., cocaine and opiates), there was no significant association between cannabis use and low birth weight

Pregnancy complications for the mother

- This subsection is broken down into the following 3 topics and informed by the following studies:
  - Stillbirth and spontaneous abortion (1 case-control study, 1 study where the design was not clearly specified, a good- or fair-quality systematic review was not identified)
  - Fetal distress (1 systematic review, good-quality primary literature published after the most recently published good- or fair-quality systematic review was not identified.)
  - Other complications (1 systematic review, 3 primary literature studies where the designs were not specified)

Neonatal conditions in infant (including admission of infant to neonatal intensive care unit)

- This subsection is broken down into the following 3 topics and informed by the following
  - Prematurity/gestational age (1 systematic review, 4 primary literature studies where the designs were not clearly specified)
  - Neonatal intensive care unit admission (1 systematic review, 1 primary literature study where the design was not clearly specified)
  - Other neonatal conditions (1 systematic review, 2 primary literature studies where the designs were not clearly specified)

Later outcomes

- This subsection is broken down into the following 7 topics and informed by the following studies:
  - Sudden infant death syndrome (1 case-control study, a good- or fair-quality systematic review was not identified)
  - Breastfeeding (1 non-systematic review, 1 study where the design was not specified, a good- or fair-quality systematic review was not identified)
  - Physical growth (1 cohort study, a good- or fair-quality systematic review was not identified)
  - Cognition/academic achievement (The number and types primary studies were not clearly specified, a good- or fair-quality systematic review was not identified)
  - Behaviour (The number and types primary studies were not clearly specified, a good- or fair-quality systematic review was not identified)
  - Substance use and delinquency (The number and types primary studies were not clearly specified, a good- or fair-quality systematic review was not identified)
  - Mental health and psychosis (The number and types primary studies were not clearly specified, a good- or fair-quality systematic review was not identified)

Psychosocial (Ch. 11)

Chapter Conclusions:

- "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)
- There is **limited evidence** of a statistical association between cannabis use and:
  - Impaired academic achievement and education outcomes
  - Increased rates of unemployment and/or low income
  - Impaired social functioning or engagement in developmentally appropriate social roles
- 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" (11-15)

Additional Chapter Notes:

- "It is difficult to document a direct link between cannabis use and negative educational outcomes, because other variables play a role."
  - "There is some evidence to suggest that a higher frequency and persistence of cannabis use is associated with some negative educational outcomes"
  - "The age at which cannabis use is initiated may be important in determining negative educational outcomes"
  - "Educational outcomes related to cannabis use tend to be confounded with the use of other substances, particularly tobacco/smoking cigarettes"

Cognition

- This subsection is broken down into 3 topics and informed by the following studies (Note: Primary literature were not used in this section as all study questions were addressed by systematic reviews)
  - Learning (3 systematic reviews)
  - Memory (3 systematic reviews)
  - Attention (4 systematic reviews)

- Learning – defined as "the wide array of function that involves the ability to observe, comprehend, absorb, and appropriate new information into an individual's cognitive repertoire (e.g., verbal, auditory, visual)" (11-2)
  - A systematic review of 11 manuscripts found "strong support of acute cannabis use on interference in learning" (11-3), primarily relying on word list learning. However, there was mixed support for sustained effects.
  - A systematic review of 9 studies assessed the sustained impact of cannabis use on learning via neuropsychological tests. Authors found a small negative effect size of -0.21 (measure of effect not stated) (99% CI= -0.39 to -0.022) for the sustained impact on learning.
  - A systematic review of 13 studies examined sustained impact on learning using neuropsychological metrics. Using the criteria of cannabis abstinence for ≥ 25 days, review authors found a very small effect size of -0.16 (measure of effect not stated) (95% CI= -0.33 to 0.02)(**Note:** this relationship is not significant)

- Memory – defined as "the wide array of function that involves the abilities to remember, temporarily store, more extensively store, process, manipulate, recall and reproduce data (e.g., verbal, auditory, written)" (11-2)
    - A systematic review of 22 studies assessed the acute impact of cannabis use on memory, including working memory and other memory functions, using various neuropsychological tests.
        - There was "moderate-to-strong evidence for acute interference of cannabis in memory"(11-4)
        - However, based on 11 studies, "there was mixed to no evidence for interference in memory functioning after cessation from cannabis use." (11-4)
    - A systematic review examined memory using 7 MRI/fMRI studies. In the included studies, abstinence ranged from 7 days to 201 days post-cannabis cessation.
        - "Although there was no difference in task performance between cannabis users and non-users, cannabis users engaged slightly different parts of their brains as compared to non-users to accomplish the task, often described in the neuroimaging literature as the utilization of 'compensatory' efforts." (11-4)
    - A systematic review examined 5 MRI/fMRI studies. In the included studies, abstinence ranged from 24 hours to 26 days.
        - "Cannabis users showed equivalent performance across neuroimaging tasks as non-users, but could have engaged 'compensatory efforts' to achieve these outcomes" (11-4)

- Attention – defined as "an individual's ability to stay focused on the task at hand without being distracted, but also cognitively flexible enough to transfer to a different task or set of information when the time requires (e.g., including brain regions relevant to visual, auditory, and verbal processing, as well as executive control)" (11-2)
    - A systematic review included 17 studies and assessed attention using several approaches (e.g., neuropsychological metrics of continuous task performance, reaction time, divided attention tasks).
        - There was strong evidence for acute interference of cannabis on attention."(11-5)
        - However, based on 10 studies, there was "mixed evidence for impairment in attention functioning after cessation from cannabis use." (11-5)
    - A systematic review included 3 studies that looked at MRI and fMRI measures.
        - There was limited evidence of differences in task performance, but as with other domains, cannabis users may be engaging different neural network to achieve similar outcomes during the task (e.g., compensatory efforts) (11-5)
    - A systematic review included 11 studies and assessed the long-term sustained relationship between cannabis use and attention following abstinence, using neuropsychological measures.
        - There was a small effect size for the influence of cannabis use on attention (effect size [ES] -0.083, 99% CI= -0.32 to 0.15)
    - A systematic review examined the sustained impact of cannabis on attention performance using neuropsychological test performance.
        - There was a small effect size for the sustained impact of cannabis on attention (ES -0.20, 95% CI= -0.49

to 0.09)

- Special note regarding developmental implications among adolescents:
  - The Committee acknowledged that within studies relating to cannabis use and cognitive function, representation of adolescents in study samples was small ("often less than 20% of the full sample, and rarely examined independently to uncover potential developmental differences in cognitive function and/or its interference between the age groups")(11-7).
  - Furthermore, adolescents were rarely examined independently to determine developmental differences between age groups.
  - More research is needed to examine the cognitive impacts among adolescents and emerging adults

Academic achievement

- This section is based on 1 systematic review, 1 cohort study, 6 studies where the designs were not clearly specified

Employment and income

- This subsection is based 8 studies where the designs were not clearly specified. No good- or fair-quality systematic reviews were identified.

Social functioning and social roles

- This subsection is based on 1 systematic review, 4 studies were the designs were not clearly specified

Mental Health (Ch. 12)

Chapter Conclusions

- "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
- There is **moderate evidence** of a statistical association between cannabis use and:
  - Better cognitive performance among individuals among individuals with psychotic disorders and a history of cannabis use
  - Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use)
  - A small increased risk for the development of depressive disorders
  - Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users
  - Increased incidence of suicide completion
  - Increased incidence of social anxiety disorder (regular cannabis use)
- 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
	• 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
	  ○ The likelihood of developing bipolar disorder, particularly among regular or daily users
	  ○ The development of any type of anxiety disorder, except social anxiety disorder
	  ○ Increased symptoms of anxiety (near daily cannabis use)
	  ○ Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder
	• There is **no evidence** to support or refute a statistical association between cannabis use and:
	  ○ Changes in the course or symptoms of depressive disorders
	  ○ The development of posttraumatic stress disorder" (12-29)
	
	Additional Chapter Notes
	• The Committee noted that co-morbidity between substance abuse and mental health disorders exist, which directly affects the ability to determine causality and/or directionality in the associations. Three most common hypotheses for this are:
	  ○ "Substance use may be a potential risk factor for developing mental health disorders
	  ○ Mental illness may be a potential risk factor for developing a substance abuse disorder
	  ○ An overlap in predisposing risk factors (e.g., genetic vulnerability, environment) may contribute to the development of both substance abuse and a mental health disorder" (12-2)
	• The Committee noted special considerations and limitations regarding the fact that the primary literature in mental health is mostly observational:
	  ○ Observational studies received a lower-quality grading in most quality assessments and there are challenges to synthesizing observational studies (compared to RCTs) given greater variety in study design and conceptualization, and less experience in applying systematic review/meta-analysis methods to observational literature (12-26)
	  ○ In assessing the body of evidence, it may not be appropriate to correlate the number of systematic reviews with the strength of evidence:
	  ▪ Systematic reviews may overlap in terms of its included studies. "The number of systematic reviews or meta-analyses may not, by themselves, indicate a stronger body of evidence" (12-27). It is also of concern when multiple reviews identify different studies (the methodology behind these differences are not always transparent)
	  ○ There are challenges with exposure assessment in observational studies (especially in the context of cannabis use given its illegal status and the use of self-reports)
	  ▪ It is difficult to assess specific details related to exposure (e.g., dose, specific chemicals, mode of intake, duration)

- Systematic reviews may include studies using greatly differing definitions related to use
- Mental health-related studies may use medical records that show a diagnosis of cannabis use disorder as a proxy for cannabis use disorder. This may lead to exposure and non-exposure groups having similar intakes of cannabis and result in misclassification bias.

Development of schizophrenia or other psychoses

- This subsection is based on 5 systematic reviews (2 reviews were discussed), 1 study where the design was not specified, 1 longitudinal study, 1 case-control study, 1 cross-sectional study

- **Systematic Reviews**
  - A systematic review/meta-analysis of 10 studies reported results for 66,816 individuals
    - To be included, studies had to assess the dose of cannabis use in at least 3 exposure groups
    - Review authors "found an association between cannabis use and psychosis (OR 3.9, 95% CI=2.84 to 5.34) among the most severe cannabis users, as compared to nonusers." (12-3)
    - There is also "a dose-response relationship with an OR of 1.97 (95% CI=1.68 to 2.31) for those at the median of any cannabis use and an OR of 3.40 (95% CI=2.55 to 4.54) for those in the top 20 per cent of cannabis use"
    - There was an association between cannabis use and:
      - The presence of psychotic symptoms (pOR 3.59, 95% CI=2.42 to 5.32)
      - A diagnosis of schizophrenia or psychotic disorder (pOR 5.07, 95% CI=3.62 to 7.09)
    - Review authors did not assess the quality of the papers included in the meta-analysis, but assessed publication bias (low) and heterogeneity (heterogeneity existed in their sample of studies)
  - A systematic review/meta-analysis of 32 studies included 11 studies that focused on cannabis use and psychotic outcomes (from 7 cohort studies)
    - "The authors found that in individuals that have ever used cannabis, there was an associated increased risk of a psychotic outcome (aOR 1.41, 95% CI=1.20 to 1.65).
    - When the analysis was restricted to frequent cannabis use, the investigators found a stronger association (aOR 2.09, 95% CI=1.54 to 2.84), suggesting a dose-response relationship between cannabis use and the risk of a psychotic outcome." (12-4)
    - "The authors noted that some individual studies adjusted for psychotic symptoms or diagnosis at baseline to help clarify the temporal order of events.
    - The authors also noted that individual studies excluded psychotic symptoms that arose solely from drug use by using scales to measure drug intoxication.
    - In addition, this group of studies collectively adjusted for approximately 60 different potential confounders, including other substance use, personality traits, sociodemographic markers, intellectual ability, and other mental health problems." (12-4)

	• **Primary Literature**
	  ○ A study examined the impact of the level of cannabis use (no use, use without impairment, abuse and dependence) on conversion to psychosis (defined as "having a psychotic level positive symptom that is either seriously disorganizing or dangerous, or that occurs for at least 1 hr/day for an average of 4 days in the past month" (12-4))
	  ▪ "In a follow-up assessment (approximately 17 months after the initial baseline assessment), the researchers found that cannabis abuse/dependence was associated with a greater risk of conversion to psychosis within the chronic high-risk population." (12-5)
	  ▪ However, when alcohol use was incorporated into the analysis, cannabis abuse/dependence was no longer significantly related to conversion (HR 1.875, 95% CI=0.963 to 3.651).
	  ○ A longitudinal study examined the association between lifetime cannabis use and the development of psychosis
	  ▪ Authors followed "182 individuals at ultra-high risk for psychosis disorder for two years and found that varying degrees of cannabis use (i.e., lifetime use, frequent use, early-onset use, and continued use after presentation) among lifetime cannabis users is associated with an increased transition to psychosis." (12-5)
	  ▪ However, "within this specific ultra-high risk population, cannabis users were no more likely to develop psychosis than those who had never tried cannabis." (12-5)
	  ○ A case-control study compared patients with first-episode psychosis and population controls
	  ▪ "First-episode psychosis patients were more likely to have lifetime cannabis use, more likely to use cannabis use everyday, and to mostly use high potency cannabis, as compared to controls." (12-5) They were also more likely to have used cannabis before age 15. Duration of use or other drug use did not differ between cases and controls.
	  ▪ Authors found an increased risk of developing psychosis in subjects who used cannabis daily (OR 3.04, 95% CI=1.91-7.76), and in subjects who used high potency cannabis (OR 2.91, 95% CI=1.52 to 3.60). A variety of confounders were adjusted (e.g., other drug and alcohol use)
	  ○ A cross-sectional study examined the association between cannabis use, the risk of psychosis, and the dopamine receptor type 2 (DRD2) polymorphism, rs1076560 and found "a significant interaction between lifetime frequency of cannabis use and DRD2 polymorphism rs1076560 on psychosis risk." (12-5)
	
	• **Additional Sub-Chapter Notes**
	  ○ "The association between cannabis use and the development of a psychotic disorder is supported by data synthesized in several good-quality systematic reviews. The magnitude of this association is moderate to large and appears to be dose-dependent, and it may be moderated by genetic factors"
	  ○ Factors contributing to the strength of evidence stemming from the cited systematic reviews include:
	  ▪ Large sample sizes
	  ▪ Relative homogeneity of the findings
	  ▪ Presence of relationships between dose/exposure and the risk
	  ▪ Adjustments for confounders within the included studies of the systematic reviews

	▪ Completed assessments for publication bias ○ Limitations of the summarized studies include ▪ Reliance of self-report for cannabis use ▪ Issues with study designs (e.g., lack of randomization) ▪ "Lack of information on the frequency of use, patterns of long-term use, and possibly confounding polysubstance effects" (12-6) ▪ Limited sample sizes and controlling for confounders (for the primary studies) ○ Ecologic data (studies of concomitant time trends) evaluating trends in cannabis consumption and diagnosis of psychosis over time were not reviewed due to limitations for drawing conclusions. **Course or symptoms of schizophrenia or other psychoses** • This subsection is broken down into the following 3 topics and informed by the following studies: ○ Positive symptoms (e.g., delusions, hallucinations, or abnormal motor behaviour): 1 systematic review, the number and types primary studies were not clearly specified ○ Negative symptoms (e.g., diminished emotional expression, lack of interest or motivation to engage in social settings, speech disturbance, anhedonia): 1 systematic review, the number and types primary studies were not clearly specified) ○ Cognition: 3 systematic reviews, 1 longitudinal study, 1 study where the design was not clearly specified • <u>Positive symptoms:</u> ○ Details not reported due to the evidence statement being labelled as limited. • <u>Negative symptoms:</u> ○ **Systematic Review:** ▪ A systematic review included 4 cohort studies (out of 13 cohort studies in the larger review) that assessed the effects of cannabis use on negative symptoms in patients with psychotic disorders • "Cannabis use was not associated with negative symptoms scores in three studies." (12-7). However, it was associated with reduced negative symptoms scores in the fourth study, although confounders or baseline differences in symptoms were not controlled for. ○ **Primary Literature:** ▪ A cross-sectional study found that compared to non-users, cannabis use was strongly associated with fewer negative symptoms of avolition-apathy (p=0.0001) ▪ A study found that in a cross-sectional analysis, past 90-day cannabis use was not associated with the severity of negative symptoms (adjusted coefficient 0.12, 95% CI=-0.05 to 0.29)" and in a longitudinal analysis, cannabis dose was not associated with negative symptom severity (adjusted coefficient, 0.18; 95% CI= -0.14 to 0.51)

- The prospective longitudinal study found "no association between cannabis dose and negative symptoms after adjustment for confounders including other drug use (adjusted coefficient, 0.28; 95% CI=-0.04 to 0.61)." (12-9)
- The case-control study found that "cannabis use at baseline or the 1-year assessment was not associated with differences in negative symptoms relative to non-users (as measured by PANSS -0.07; 95% CI=-1.11 to 0.97)" (12-9)

- <u>Cognition</u>
  - **Systematic Reviews:**
    - All 3 systematic reviews assessed the relationship between cannabis abuse/dependence and cognition effects in patients with psychotic disorders.
    - A systematic review of 19 studies (3 of which focused on cannabis use) found that among patients with schizophrenia and/or schizoaffective disorders, cannabis users performed better on various measures of cognition than non-cannabis users (12-7)
      - Statistically significant associations were found between cannabis use and:
        - Verbal learning and memory (Hedges g 0.351, 95% CI=0.179 to 0.523) **Note:** "Hedge g reports the unbiased estimate of the effect size (the standardized difference between two means). It is commonly used for small sample sizes)" (12-7)
        - Attention and psychomotor speed (Hedges g 0.316, 95% CI=0.144 to 0.488)
        - Global cognitive factor (Hedges g 0.237, 95% CI=0.083 to 0.390)
      - "Tests of associations with working memory or executive function were not statistically significant" (12-7)
    - Another systematic review/meta-analysis involving patients with schizophrenia found "moderate associations with cannabis users performing better on general cognitive ability and intelligence; selective, sustained and divided attention; and visual-spatial and constructional abilities." (12-8)(Note: effect sizes not provided)
    - A third systematic review/meta-analysis of 10 studies involving patients with schizophrenia found that "patients with established schizophrenia and a history of cannabis use showed better performance on tests assessing cognitive abilities than did patients who did not use cannabis." (12-8)
      - An analysis on global cognition showed small to moderate increases in performance in cannabis users compared to non-users (Cohen's d 0.35, 95% CI=0.09 to 0.61; p=0.009) **Note:** "Cohen's d is an estimate of the effect size (the standardized difference between two means)" (12-8)
      - Cannabis users also showed better performance (small to moderate statistically significant effects) in processing speed, visual memory, and planning, despite the smaller number of studies available for these comparisons
      - "No differences were reported for assessments of attention, verbal memory or working

memory." (12-8)

- **Primary Literature:**
  - A study found that among patients diagnosed with psychotic disorder, there was "no association between lifetime cannabis use or cannabis dependence and cognitive function after controlling for confounding variables including the onset of illness and co-morbid cognitive functioning" (12-9)
  - A longitudinal study of patients with schizophrenia found "a negative effect of longitudinal cannabis use in the social cognition domain (Pearson correlation, -0.34; $p<0.05$)" (12-9)
  - A study found that cannabis use before the onset of psychosis results in molecular interactions that affect patient reaction time and accuracy.

- Additional Sub-Chapter Notes
  - Overall, the data supports that cannabis use does not worsen negative symptoms in patients with psychotic disorders
  - Overall, data supports that a history of, but not recent, cannabis use is associated with statistically significant performance improvement on measures of cognitive function in patients with psychotic disorders
    - "It is not clear how the differences in scores might translated with respect to overall improved outcomes in functioning beyond the test setting" (12-10)
    - Other data do not support the notion that acute cannabis exposure improves cognitive performance in patients with psychotic disorders (i.e., Results from Chapter 11 demonstrate that acute intoxication is associated with impairments in learning, memory, and attention)
    - Potential explanations of data indicating better performance on certain measures of cognition in patients using cannabis:
      - "Patients represent a higher-functioning subgroup of psychotic patients
      - Cannabis users who achieve abstinence have better premorbid cognitive status
      - A history of cannabis use may have exerted neuroprotective effects in patients with psychotic disorders" (12-10)

Development of bipolar disorder or mania

- "Bipolar and related disorders are categorized by episodes and/or symptoms of mania, hypomania, and depression" (12-11)
- This subsection is based on 1 systematic review, and 2 primary literature studies where the designs were not specified.

Course or symptoms of bipolar disorder

- This subsection is based on 1 systematic review and 2 longitudinal studies

Systematic Review

- A systematic review of 3 studies assessed the relationship between cannabis use and the course, symptoms or other endpoints in individuals with bipolar disorder.
    - "Cannabis use may worsen the course of bipolar disorder by increasing the likelihood, severity, or duration of manic phases." (12-13)
        - "The duration of active cannabis use was associated with duration of mania syndrome/symptoms
        - Cannabis use within a quarter (3-month time period) was associated with manic symptoms or episodes
        - 'Any cannabis use' was associated with mania symptoms over 1 year in a sample of 3,426 in- and outpatient patients" (12-13)

Primary Literature

- A longitudinal study found that:
    - Previous cannabis users had similar outcomes to never users ($p>0.05$).
    - "Current users had lower rates of recovery ($p=0.004$) and remission ($p=0.014$) and higher rates of recurrence of bipolar disorder ($p=0.014$)" (12-13)
    - "The median time to remission was longer in the current cannabis use group (571 days, 95% CI=539 to 588) compared with the other two groups (never users: 236 days, 95% CI=209 to 345; previous users: 189 days, 95% CI=1.5 to 357)" (12-31)
    - "The times to relapse and recurrence were shorter in current use group" (12-13)
    - Compared to no cannabis use, cannabis use was associated with:
        - Time to recovery (HR 0.53, 95% CI= 0.298 to 0.959)
        - Relapse (HR 1.61, 95% CI= 1.116 to 2.316)
        - Recurrence (HR 1.67, 95% CI= 1.206 to 2.32)
    - However, when confounders (i.e., alcohol and other substance use variables) were added in the analysis above, only time to recurrence remained statistically associated with cannabis use (HR 1.47, 95% CI=1.030 to 2.092)
- A longitudinal study examined weekly cannabis users and almost daily cannabis users
    - Authors found "a steady association with the incidence of mania/hypomania symptoms in all adjusted models (OR 2.47, 95% CI=1.03 to 5.92)
    - In contrast, daily cannabis use was not associated with mania/hypomania symptoms (OR 0.52, 95% CI=0.17 to 1.55)" (12-13)

Development of depressive disorders or symptoms

- This subsection is based on 2 systematic reviews (the most recent systematic review was discussed) and 7 primary literature studies where the designs were not specified (specific study results were not reported).

Systematic Review

- The most recent systematic review identified 14 studies collecting longitudinal and prospective data, and found:

- "Cannabis use was associated with a small increase in risk for depressive outcome (pOR 1.17; 95% CI=1.05 to 1.30)" (12-15)
- "The analysis further revealed a dose-response relationship, with a slightly higher OR observed in 7 studies comparing heavy cannabis use to non-cannabis users (pOR 1.62; 95% CI=1.21 to 2.16)" (12-15)
- The review studies varied in: sample sizes, ages, exposure assessment, use of a comparator group, whether or not confounding was controlled for.

Primary Literature:

- "Although several primary research studies found a positive association, the confounding factors of polydrug use or unspecified cannabis use made it difficult for the committee to make conclusions on overall findings" (12-15)
- "Additional studies reviewed provided mixed findings on the association between cannabis use and depression or depressive symptoms. A consideration of the confounding factors led to several of these mixed findings" (12-15, 12-16)
- For example, a primary literature study examined 3 longitudinal studies "to determine the association between maximum frequency of cannabis use before age 17 and seven developmental outcomes, including depression" (12-16):
  - "The outcomes of depression were assessed by different measures…and at different ages across the three studies" (12-16)
  - "The investigators of this study created a dichotomous measure of moderate or severe depression in the past week to the past month between ages 17 and 25 years." (12-16)
  - "After adjusting for study-specific effects, investigators found a significant association between adolescent cannabis use and the study's measure of depression." (12-16)
  - Investigators also found an apparent potential dose-response relationship:
    - Less than month use (OR 1.12, 95% CI=1.01 to 1.25)
    - Monthly or more (OR 1.26, 95% CI=1.02 to 1.56)
    - Weekly or more (OR 1.42, 95% CI=1.03 to 1.94)
    - Daily use (OR 1.59, 95% CI=1.04 to 2.42)
  - "However, after adjusting for relevant covariates in the analysis, this association became insignificant and negligible in size" (12-16)
  - "The authors noted that the confounding factors spanning the individual's background and functioning as well as parental and peer factors likely affected the change in the research findings" (12-16)

Course or symptoms of depressive disorder

- No good- or fair-quality systematic review, or good-quality primary literature published after the most recently published good- or fair-quality systematic review were identified.

Suicide, suicide attempts, suicidal ideation

- This subsection is based on 2 systematic reviews (the most recent one was discussed) and 1 study where the design was not clearly specified.

- **Systematic Review**
  - The most recent systematic review examined the relationship between acute and chronic cannabis use, and suicidal ideation, suicidal attempts, and suicide. The review included 12 studies (2 case-control studies, 2 longitudinal studies, other study designs not clearly stated); a subset of the studies were meta-analyzed
    - Cannabis exposure was defined as follows:
      - Any cannabis use: life-time use, use before or at age 15, ever used, any use in past month, any use in last year
      - Chronic use: cannabis use patterns, symptoms of cannabis use disorder, heavy cannabis use
      - Heavy cannabis use: used ≥40 times, DSM-IIIR abuse/dependence, ≥6 times/month, >11 times in past year, >10 times, daily
    - Results from multiple meta-analyses revealed that:
      - Any cannabis use was associated with an increased risk of suicidal ideation (pOR 1.43, 95% CI=1.13-1.83)
      - Heavy cannabis use was also associated with a larger increase of suicidal ideation (pOR 2.53, 95% CI=1.00 to 6.39) (**Note:** this relationship is not significant)
      - Any cannabis use was associated with an increased risk of suicide attempts (pOR 2.23, 95% CI=1.24 to 4.00)
      - Heavy cannabis use was associated with a higher risk of suicide attempt (pOR 3.20, 95% CI=1.72 to 5.94)
      - Any cannabis use was associated with an increased risk of death by suicide (pOR 2.56, 95% CI=1.25 to 5.27)

- **Primary Literature**
  - A longitudinal study used a general population sample of an epidemiologic survey and found that:
    - "Any cannabis use in Wave 1 (baseline) was not statistically significantly associated with increased risk for developing suicidality in Wave 2 (follow-up) (aOR 1.56, 95% CI=0.98 to 2.46)" (12-18)
      - When results were stratified by gender (in fully adjusted models), researchers found significant differences in risk for suicidality. Cannabis use was significantly associated with the incidence of suicidality in men (aOR 1.91, 95% CI=1.02-3.56) but not women (aOR 1.19, 95% CI=0.64-2.20)
    - "The magnitude of the relationship with the 3-year incidence of suicide ideation is larger in men (aOR 4.28, 95% CI=1.32 to 13.82) who are daily cannabis users, but this pattern is not observed for women (aOR 0.75, 95% CI=0.28 to 2.05). However, in adjusted models, neither cannabis use (aOR -1.91, 95% CI=0.85 to 4.28), nor daily cannabis use (aOR 1.31, 95% CI=0.42 to 3.05) was statistically significantly associated with the incidence of suicide attempts"
    - Sex moderated the association between cannabis use (especially daily use) and suicide attempts

- **Additional Sub-Chapter Notes**
  - "The studies presented demonstrate evidence of a dose-response effect, with heavy cannabis use being associated with a higher risk of suicidal ideation and suicide attempts" (12-19)
  - "Sex differences emerged from the research findings related to suicidality and death by suicide. These sex differences may have occurred due to differences in where the study samples were recruited or how the data were assessed" (12-19)
  - Limitations of the evidence include:
    - "Lack of homogeneity in measurement of cannabis exposure
    - Lack of systematic controls for known risk factors
    - Short period of observation for suicidality
    - Variability in covariates used to adjust for confounders
    - Differences in dose-response analyses" (12-19)
    - Small sample sizes
    - Not all studies adjusted for alcohol and other co-morbidities

Development of anxiety disorders

- This subsection is based on 1 systematic review, 3 longitudinal studies, 1 cohort study, and 3 studies where the designs were not clearly specified

- **Systematic Review**
  - The systematic review of 5 longitudinal studies (four focused on adolescents, one on general population) assessed the relationship between cannabis use and anxiety disorders
    - All component studies adjusted for confounders (e.g., demographics, prior anxiety disorder diagnosis, alcohol and tobacco use, other mental health problems at age 15)
    - Review authors found that "cannabis use at baseline was associated with the development of symptoms of anxiety at follow-up (OR 1.28, 95% CI=1.06 to 1.54), after adjusting for confounders (e.g., other substance use, psychiatric comorbidity, certain demographics)" (12-20)

- **Primary Literature**
  - Three studies used the same nationally representative sample of adults aged 18+
    - The first study investigated the prospective associations of cannabis use in the past year with anxiety disorders 3 years later
      - After adjusting for covariates, authors found that past-year cannabis use was not associated with an increased prevalence of anxiety disorders (OR 1.0, 95% CI=0.8 to 1.2), panic disorder (OR 0.8, 95% CI=0.5 to 1.2), social anxiety disorder (OR 1.2, 95% CI=0.8 to 1.8), specific phobia (OR 0.9, 95% CI=0.7 to 1.2), generalized anxiety disorder (OR 1.0, 95% CI=0.7 to 1.4) assessed 3

	years later. There was also no significant relationship between cannabis use and incident anxiety disorders (aOR 0.9, 95% CI=0.7 to 1.1) • Authors found a statistically significant association between increased frequency of cannabis use and increased odds of incident social anxiety disorder (OR 1.8, 95% CI=1.1 to 2.8) • Study limitations include: the use of self-reported to determine cannabis exposure, possibility of residual confounding, follow-up period was limited to 3 years ▪ In the second study: • After adjusting for covariates, the authors found no association of cannabis use with the increased incidence of any anxiety disorder (aOR 1.12, 95% CI=0.63 to 0.98) • Authors also found a statistically non-significant association between daily (or almost daily) use of cannabis and the incidence of social anxiety 3 years later (aOR 1.98, 95% CI=0.99 to 6.98). However, this relationship was found to be significant in older adults (aOR 2.83, 95% CI=1.26-6.35), but not for younger adults (aOR 1.76, 95% CI=0.44 to 6.98) • Authors found "a statistically significant relationship between cannabis use disorder and incident social anxiety disorder among young adults (aOR 2.45, 95% CI=1.19 to 5.06), but not older adults (aOR 1.38, 95% CI=0.58 to 3.25)" (12-21) ▪ The third study examined past-year regular cannabis use (at least weekly use) and current as well as prospective presence of anxiety disorders 3 years later • "Authors found no association (OR 1.09, 95% CI=0.90 to 1.32) in the prospective analyses that adjusted for psychiatric comorbidity and sociodemographic factors" (12-21) • However, when looking at specific anxiety disorders, statistically significant associations were found between regular cannabis use and: ○ An increased risk of developing panic disorder with agoraphobia (OR 1.56, 95% CI=1.11 to 2.19) ○ Social phobia (OR 1.89, 95% CI=1.54 to 2.32) • Study limitations include: non-randomized study design, limited power to detect effects, relatively short time period of observation ▪ A cohort study found no differences among cannabis trajectory groups related to a lifetime diagnosis of anxiety disorders for black or white men after adjusting for confounders • Trajectory groups were categorized as: low/non-users, adolescence-limited users, increasing users, early onset users • Study limitations include: the possibility of selection effects, the use of self-report to assess cannabis exposure, potentially non-generalizable results (i.e., use of a limited sample of cannabis users from one geographic area, only including white and black men) ○ A longitudinal study found no evidence of an association between cannabis use at age 16 and anxiety disorder at age 18 after adjusting for pre-birth and childhood confounders (aOR 0.96, 95% CI=0.75 to 1.24) ○ A study assessed urban African American and Puerto Rican participants.

	▪ Authors found "participants with joint chronic cannabis, tobacco, and alcohol use were at an increased risk for generalized anxiety disorder in adulthood when compared to those with occasional alcohol use and no smoking or no cannabis use (OR 4.35, 95% CI=1.63 to 11.63)" (12-22) ○ A study on a large community-based sample examined joint chronic cannabis, alcohol, and cigarette use with generalized anxiety disorder ▪ When compared to individuals who occasionally use alcohol but not cigarette or cannabis use, chronic or moderate-to-heavy users of cannabis, alcohol, and cigarettes had a statically significantly increased the risk for generalized anxiety disorder (aOR 6.39, 95% CI=2.62 to 15.56) • **Additional Sub-Chapter Notes** ○ "Studies examining the relationship between cannabis use and anxiety disorder show mixed results depending on: ▪ Whether they assessed the development of anxiety symptoms or the incidence of anxiety disorder ▪ Whether the explanatory variable was any cannabis use or cannabis use disorder ▪ Whether there were adjustments for psychiatric comorbidity and sociodemographic factors" (12-22) ○ Limitations of the studies include: ▪ Use of self-report to assess cannabis exposure ▪ Possibility of residual confounding ▪ Follow-up period was limited to 3 years ▪ High loss in follow-up ▪ Limited power to detect small effects **Course or symptoms of anxiety disorders** • The subsection is based on 1 prospective study. A good- or fair-quality systematic review was not identified. **Development of Posttraumatic Stress Disorder (PTSD)** • No good- or fair-quality systematic review, or good-quality primary literature published after the most recently published good- or fair-quality systematic review were identified. **Course or symptoms of PTSD** • This subsection is based on 1 cohort study; 1 matched, case-control, cross-sectional study; and 3 other studies where the design was not clearly specified. A good- or fair-quality systematic review was not identified. **Problem Cannabis Use (Ch. 13)** **Chapter Conclusions:** (Note: This chapter contains multiple conclusions related to problem cannabis use, including the associated risk factors. Only the conclusions relevant to the research question are captured)

- "There is **substantial evidence** that:
  - Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use" (13-15)
- "There is **substantial evidence** of a statistical association between:
  - Increases in cannabis use frequency and the progression to developing problem cannabis use" (13-15)
- There is **moderate evidence** that:
  - During adolescence the frequency of cannabis use is a risk factor for the development of a problem cannabis use

Additional Chapter Notes

- The Committee notes that "the literature is unclear on the association between cannabis use and the progression to the sort of cannabis use determined to be "problem" use. A major contributor to this issue is the lack of official distinction between "risky" or "problem" use of cannabis." (13-2)
- This chapter uses "the broad term 'problem cannabis use disorder' to encompass various levels of hazardous or potentially harmful cannabis use patterns, including those related to CUD, dependence, and abuse." (13-2)

Characteristics of cannabis use associated with progression to developing problem cannabis use

- This subsection is based on 4 studies where the designs were not stated. A good- or fair-quality systematic review was not identified. (Note: only the studies with reported information that is relevant to the research question are reported below.)

- An analysis of two waves (Wave 1-baseline, Wave 2-follow-up) of a nationally representative sample of U.S. adults ages 18 years and older found that "cannabis use reported during the first wave was significantly associated with any cannabis use disorder during the second wave (aOR 9.5, 95% CI=6.4 to 14.1)" (13-2)
- Another study used the same survey data above to examine the impact of cannabis use frequency and the development of cannabis use disorder
  - "Among the past-year weekly nondependent cannabis users in Wave 1 (n=435), 9.7% progressed to cannabis dependence in Wave 2; however, an increased frequency of cannabis use per day only weakly predicted progression of cannabis use to CUD (OR 1.08. CI=1.04 to 1.13) in a prospective analysis" (13-2, 13-3)
  - "A cross-sectional analysis of Wave 1 data found that 8.0% of respondents who reported using cannabis at least once in the past year met the criteria for dependence, whereas among weekly and daily cannabis use smokers, 17.0% and 18.8%, respectively, met the criteria for dependence" (13-3)
- Data from 2 large U.S. surveys were analyzed to assess the "rates of cannabis use disorder as a function of biological sex, ethnicity, and frequency of cannabis use"(13-3)
  - Authors found that "the overall prevalence of DSM-IV cannabis abuse and dependence increased significantly from 1.2% to 1.5% between 1991 and 2001." (13-3)
  - "The increase in the rates of cannabis use disorder among cannabis users was observed in the absence of self-reported increases in frequency or quantity of use (p=0.002) suggesting that the increases in CUD may be due to

	the increased potency of cannabis between 1991 and 2001"(13-3)
	• Reports authors noted several limitations of the studies:
	  ○ The data relied on self-reports which requires individuals to have insight into what constitutes as problematic cannabis use
	  ○ The frequency of used in the studies did not account for the amount of cannabis used per occasion, which is thought to be a key contributor to rates of developing problem cannabis use
	  ○ The data may not reflect the current level of risk given that cannabis potency has increased and different routes of administration are becoming popularized
	
	Risk and Protective Factors for Developing Problem Cannabis Use
	• This subsection is broken down into multiple topics (e.g., anxiety, psychopathology, biological sex). Only topics were relevant to the research question and extracted on:
	  ○ Age of initiation of cannabis use: information based on 1 longitudinal study and 3 studies where the designs were not specified. A good- or fair-quality systematic review was not identified).
	  ○ Other variables specific to adolescents (i.e., cannabis use frequency): relevant information based on 1 cohort study, 1 longitudinal study
	
	• <u>Age of initiation of cannabis use</u>
	  ○ One study analyzed data from a survey of a representative sample of U.S. residents aged 12 and older
	  ▪ "Adolescent onset cannabis users were more likely to become dependent than respondents who had initiated cannabis use during adulthood" (13-8)
	  ▪ "Using data obtained from adult onset users of cannabis (21 years of age and older) as a reference, [the authors] found a strong association between an onset of cannabis use between 11 and 13 years of age and the relative risk of becoming dependent (aRR 10.8, 95% CI=2.5 to 47.1)" (13-8)
	  ▪ "The estimated risk ratio of developing cannabis dependence when initiating cannabis use at 14-15 years of age was 12.0 (95% CI=2.9 to 50.3)" (13-8)
	  ○ A study used data from 3 long-running surveys to explore the relationship between early, frequent cannabis use and the development of cannabis use disorder
	  ▪ "Compared to individuals who had never used cannabis, those who were daily users before 17 years of age had significantly greater odds of later developing cannabis dependence (aOR 17.95; 95% CI=9.44 to 34.12)". (13-8) Covariates, such as sociodemographic factors and other potential antecedents to the development of problem cannabis use, were controlled for.
	  ○ A longitudinal study surveyed a community-based sample of adolescents and young adults between 14 and 24 years of age over a 10-year period (with 4 waves of assessments)
	  ▪ "During the first assessment (at baseline), 1.5% of the sample met the criteria for DSM-IV cannabis dependence. Among those who reported using cannabis at that time, 4.3% met the criteria for dependence. At the 10-year follow-up, 6.1% of those reported using cannabis at baseline met the

criteria or dependence." (13-8)
        - "The authors concluded that the higher rates of cannabis dependence during the 10-year follow-up assessment suggested that cannabis use early in life may be indicative of increased vulnerability to developing CUD. However, there are other factors that may explain why an increase in cannabis dependence was observed at the 10-year follow up." (13-8)
    - The data above was used in another study that "evaluated the probability and speed of going from first cannabis use to developing cannabis dependence as a function of the age of first use."
        - "The conditional probability of transition from cannabis use to dependence was estimated to be 6.2%." (13-8)
        - The authors found that compared to those with alcohol or nicotine use disorders, "the transition from first cannabis use to the development of CUD occurred at a faster rate" (13-8)

- <u>Other variables specific to adolescents (i.e., cannabis use frequency):</u>
    - In a 10-year representative cohort study, the frequency of cannabis use was evaluated to determine the association between cannabis use by 18 years of age and risk for CUD at 24 years of age
        - The study involved "six surveys during adolescence (15-17.5 years of age) and two follow-up assessments during young adulthood (at 21 and 24 years of age)" (13-9)
        - "One-third of the population reported having used cannabis during adolescence, and 37 per cent of the adolescent cannabis users were using at least weekly when interviewed at 24 years of age" (13-9)
        - "After adjusting for potential confounding factors, problem cannabis use at 24 years of age was associated with adolescent cannabis use, tobacco use, and persistent mental health problems" (13-9, 13-10)
    - In a follow-up analysis, the frequency of cannabis use was evaluated "to determine whether moderation of cannabis use among adolescent cannabis users protected against the risk of CUD in young adulthood." (13-10)
        - "While 31% of the population reporting having ever used cannabis, 71% of occasional users and 28% of weekly users were abstinent in young adulthood" (13-10)
        - "Adolescent weekly or daily users who persisted with regular use (rather than decreased use or becoming abstinent) were at greatest risk for developing CUD in young adulthood." (13-10)
        - "This suggests that moderating adolescent cannabis use can protect against the later problem use that is observed in persistent users" (13-10)
        - "However, regardless of whether the adolescent users moderated their intake, the risk for developing CUD in young adulthood was still significantly greater for adolescent users than for those who never used cannabis" (13-10)
    - Data from a longitudinal survey of a representative sample of secondary students were assessed to determine adolescent precursors of young adult cannabis dependence
        - The sample was assessed for cannabis disorders 6 times between the ages of 14 and 17, and again at 20 years of age
        - Variables that independently predicted cannabis dependence in young adulthood included regular

cannabis use during adolescence (weekly use: OR 4.9; daily use: OR 4.6; p=0.02)
    - "Regular cannabis use during adolescence only increased the risk for CUD in the absence of persistent problem alcohol use" (13-10)

Abuse of other substances (Ch. 14)

Chapter Conclusions

- "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
- There is **limited evidence** of a statistical association between cannabis use and:
    - The initiation of tobacco use
    - Changes in the rates and use patterns of other licit and illicit substances" (14-12)

Development of substance dependence and/or a substance abuse disorder

- This subsection is broken down into the following 3 topics and informed by the following studies:
    - Alcohol (1 longitudinal study, a good- or fair-quality systematic review was not identified)
    - Tobacco/Nicotine (1 longitudinal study, 1 cohort study, no good- or fair-quality systematic review)
    - Mixed Drug use (2 longitudinal studies, 1 cohort study, no good- or fair-quality systematic review)

- <u>Alcohol</u>
    - A longitudinal study assessed the long-term effects of cannabis use on alcohol problems and alcohol use disorder (AUD)
        - "The researchers followed a sample of 160 female-male sibling pairs from high-risk families (sample total 320 individuals) from ages 3-5 to 21-23, assessing the participants every 3 years" (14-4)
        - Researchers collected data on age of first use, quantity, and frequency of alcohol, cannabis, and nicotine
        - The authors found that a higher frequency of cannabis use was related to greater odds of:
            - Developing drinking problems (β 0.55; SE=0.08; $p<0.05$)
            - Meeting an AUD diagnosis (β 0.59; SE=0.09; $p<0.05$)
        - The odds on developing drinking problems and meeting an AUD diagnosis were not as high when comparing the frequency of cannabis consumption to that of alcohol consumption
        - Early onset of cannabis use was not found to contribute to AUD
        - A major study limitation was the limited generalizability of study results (participants included "children who had intact families in early childhood, families that were at high risk for developing AUD, families of minority race/ethnicity" (14-8))

- <u>Tobacco/Nicotine</u>

- A longitudinal study examined "the role of cannabis use in adolescence and the likelihood of developing nicotine dependence and initiating daily tobacco smoking at an earlier age" (14-8)
  - Survey data were collected from 90,118 students.
  - "A subsample of participants was followed up at three points with more in-depth survey, a baseline survey (wave I) and two subsequent surveys (wave II one year after baseline, wave III six years later)" (14-8)
  - Authors found that:
    - "Regular lifetime users of cannabis at wave I were more likely to develop lifetime nicotine dependence (t 2.3 p<0.05; aOR 1.89, 95% CI=1.09 to 3.30) than non-users" (14-8)
    - Experimental and regular users in the past-month at wave I were more likely to develop lifetime nicotine dependence (t 2.3 p<0.05; aOR 1.83, 95% CI=1.08 to 3.11)
    - Among lifetime users, those who began using at later ages (23-27) were less likely to develop nicotine dependence at wave III compared to those who began using at earlier ages (t -3.3 p<0.01; aOR 0.82, 95% CI=0.73 to 0.93)
    - Study limitations include: self-reported data on substance use, recall bias
- A cohort study studied women cannabis users and patterns of smoking and nicotine dependence
  - After adjusting for covariates, the results indicate that women with a prior history of cannabis use were 2.8 times more likely to transition from regular smoking to nicotine dependence (HR 2.80, 95% CI=1.84 to 4.26)
  - Study limitations include: lack of generalizability to men, self reported data on substance use, recall bias

- <u>Mixed drug use</u>
  - A longitudinal study of a nationally representative sample of adults examined the association between cannabis use and the risk of developing substance abuse and other mental health disorders
    - The study compared cannabis use in the past year (wave I) with a range of substance-use related disorders 3 years later (wave II)
    - After adjusting for covariates, cannabis use in the past year was associated with an increased risk of developing:
      - Any substance use disorder, including cannabis use disorder (aOR 6.2, 95% CI=4.1 to 9.4)
      - Any alcohol use disorder (aOR 2.7, 95% CI=1.9 to 3.8)
      - Alcohol abuse (aOR 1.5, 95% CI=1.1 to 2.0)
      - Alcohol dependence (aOR 1.9, 95% CI=1.4 to 2.7)
      - Other drug use disorder (aOR 2.6, 95% CI=1.6 to 4.4)
      - Other drug abuse (aOR 3.4, 95% CI=2.5 to 5.4)
      - Other drug dependence (aOR 2.7, 95% CI=1.6 to 4.5)
      - Nicotine dependence (aOR 1.7, 95% CI=1.2 to 2.4)
  - A longitudinal study (comprised of 2 waves) assessed substance use experiences of individuals aged 12-25 and

found that:

- Compared to those who did not use cannabis, those who used cannabis more than once in their lifetime (without meeting a diagnosis of cannabis substance use disorder) were at greater risk of alcohol abuse/dependence (OR 3.44, 95% CI=1.93 to 6.12) and tobacco dependence (OR 4.12, 95% CI=2.26 to 7.51)
- Individuals diagnosed with cannabis use disorder had higher odds of being diagnosed with alcohol abuse/dependence (OR 8.78, 95% CI=3.15 to 24.53) and tobacco dependence (OR 8.61, 95% CI=3.15 to 23.56)
- Once the above models were adjusted for individual's involvement with alcohol and tobacco, the odds ratios no longer reached significance
- Compared to those who had used cannabis more than once in their life time but did not have a cannabis use disorder, those with cannabis use disorder were not at a higher risk for alcohol abuse/dependence (OR 1.77, 95% CI=0.54 to 5.78) or tobacco dependence (OR 2.61, 95% CI=0.78 to 8.72)

- A cohort study "explored factors associated with illicit drug use, abuse, or dependence among 1,265 study participants aged 16 to 25" (14-11)
  - Cannabis use data were collected for each year and classified into four levels of frequency, "did not use cannabis," "used less than monthly on average (1-11 times)," "used at least monthly on average (12-50 times)," and "used at least weekly (>50 times)" (14-11)
  - The authors found that across age groups, "annual frequency of cannabis use was the strongest predictor of illicit drug use (β 1.58, SE=0.06, p<0.0001) and drug abuse or dependence (β 1.73, SE=12, p<0.0001)" (14-11)
  - Among individuals who used cannabis at least weekly, the risk of illicit drug use is as follows (stratified by age):
    - Age 16-17: OR 92.20 (95% CI= 46.53 to 182.72)
    - Age 20-21: OR 26.31 (95% CI=17.50 to 39.69)
    - Age 24-25: OR 7.53 (95% CI=4.48 to 12.43)
  - Among individuals who used cannabis at least weekly, the risk of illicit drug abuse/dependence is as follows (stratified by age):
    - Age 16-17: OR 117.92 (95% CI= 26.31 to 523.74)
    - Age 20-21: OR 27.61 (95% CI=11.24 to 67.90)
    - Age 24-25: OR 6.49 (95% CI=2.19 to 19.20)
  - Study limitations include: questions about the generalizability of data, use of self-reported data, wide confidence intervals for some results

- <u>Additional Sub-chapter Notes</u>
  - "Most studies reviewed indicate an association between cannabis use and use of or dependence on other

	substances, with some data indicating this effect is more pronounced in younger individuals and is dependent on dose or frequency of cannabis use." (14-11) ○ Strengths of some studies cited: ▪ Longitudinal cohort studies ▪ Large sample sizes ▪ Adjustments made for variety of confounders ○ Study limitations include: ▪ Use of self-report to assess cannabis use ▪ Recall bias ▪ Limited duration of follow-up in some cases
Limitations	• In order to manage report scope, certain health outcomes may have been excluded during the literature search due to a process used to reduce the number of total articles for review. • The Committee notes that they were "not tasked to conduct a systematic review, which would have required a lengthy and robust series of processes." (B-8) However, the Committee adopted 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 ○ Pre-specification of the questions of interest before conclusions were formulated ○ Standard language to allow comparisons between conclusions ○ Declarations of conflict of interest via the National Academies conflict of interest policies" (B-8) • The Committee noted that it is possible that some literature may have been missed due to the practical steps to manage the scope of the literature within the time frame available. (B-8) • The Committee noted that very good research may not be reflected in this report because it did not directly address the health endpoint questions that the committee formulated. (B-8) • The Committee outlined special considerations for the report (1-9, 1-10): The vast majority of literature (e.g., systematic reviews, primary literature) reviewed for non-therapeutic effects consists of observational studies. This presents challenges: ○ Difficulties in assessing cannabis exposure: ▪ "Assessment of cannabis exposure is particularly challenging because of its illegal status (in most settings) and the reliance on self report" ▪ There are difficulties in accurately assessing the exposure (e.g., dose, types of products used, mode of intake, mode of intake), presenting variability in definitions for operationalizing exposure ▪ Presence of confounders related to polysubstance use ○ Variability in populations (e.g., different age groups, cannabis use history) ○ Lack of longitudinal assessments ○ Small study cohorts ○ Broad reporting standards as compared to quantitatively-based systematic examinations

Lower-risk cannabis use guidelines: A comprehensive update of evidence and recommendations	
General Information and Quality Rating	
Type of Article	Guideline
Author(s) and Date	Fischer B, Russell C, Sabioni P, van den Brink W, Le Foll B, Hall W, Rehm J, Room R (August 2017)
Country	Canada
Quality Rating	3/7 (Using Agree II Online Guideline Appraisal Tool)
Details of the Guideline	
Objective(s)	1. To review and update the evidence on modifiable behavioural factors that determine adverse health outcomes from cannabis use, and translate this evidence into a public health intervention tool (Note: this article updates recommendations from an older Lower-Risk Cannabis Use Guideline)
Databases Searched	• Medline, Embase, PsycINFO, Cochrane Library for Systematic Reviews (Note: As part of the search strategy, the authors consulted a review by the World Health Organization, *The health and social effects of nonmedical cannabis use (2016)* and the US National Academies of Sciences, Engineering, and Medicine, *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research (2017*))
Search Period	• January 1, 2010 to December 30, 2016

Inclusion/Exclusion Criteria	**Criteria for all topics:**
	<u>Inclusion criteria:</u>
	• Systematic review or meta-analysis
	• "Date of publication: from 2010 onwards" (Appendix B)
	• "Focused on cannabis only OR present clear separate outcomes for cannabis or cannabinoid products" (Appendix B)
	<u>Exclusion criteria:</u>
	• "Study is focused on showing effects of concurrent use of cannabis and other drugs" (Appendix B)
	• "Study is focused on showing beneficial effects of medical marijuana" (Appendix B)
	• "Poor report on cannabis use outcomes (e.g., data not available, cannabis effects are presented within other drugs" (Appendix B)
	
	Criteria for specific topics:
	• "Early Use Initiation
	  ○ The study shows association between age of initiation and risks/ harms of cannabis use; AND/ OR
	  ○ Study shows neurological or morphological or psychological outcomes associated with age of use.
	• Choice of Cannabis Products
	  ○ Study presents effects/ adverse events clearly related to one or more described forms of cannabinoids products (synthetic cannabinoids, TCH, CBD, etc.); AND/ OR
	  ○ Study presents relationship between dose of cannabinoid product and effects/ adverse events.
	• Cannabis Use Practices

	○ The study presents outcomes associated with one or more ways of consuming cannabis; ○ The risks are quantified and reasonably discussed. • Frequency/Intensity of Use ○ Outcomes are directly related to frequency/ intensity of use; ○ Clear report of frequency/ intensity of cannabis/ cannabinoids use. • Cannabis Use and Driving ○ Study presents association between acute cannabis use and risks/ harms of driving or operating machinery under effects of cannabis; ○ Quantitative or qualitative report on how cannabis impairs driving / operating machinery. • Special Risk Populations ○ Study shows association between the risks/ harms of cannabis use in one or more specific population (e.g. pregnancy, schizophrenia, etc.)" (Appendix B)
Article Prioritization During Relevance Screening	• Not applicable
Number and Types(s) of Articles Included	• The number of articles was not provided • The authors searched "primarily for systematic reviews and meta-analyses, and additional evidence" (e1)
Quality Appraisal Process and Results	• Authors "quality-graded the resulting evidence according to a widely used grading scheme". (e3) Two references were cited with respect to the grading scheme: ○ *Going from evidence to recommendations* (Guyatt et al., 2008) ○ *From evidence to recommendations: transparent and sensible* (GRADE Working Group, 2017 • More specific information on the quality appraisal process for individual studies was not provided (e.g., types of critical appraisal tools used) • Quality assessment scores for each included article were not provided
Strength of Evidence Assessment	• The article used the same evidence grading criteria as the National Academies of Sciences, Engineering, and Medicine in the report, *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research:* a) **"Conclusive:** based on good-quality studies and no credible opposing findings b) **Substantial:** based on several supportive findings from good-quality studies with few opposing studies c) **Moderate:** based on several supportive findings from good- to fair-quality studies with few or no credible opposing findings; a general conclusion can be made, but limitations, including chance, bias, and confounding factors, cannot be ruled out d) **Limited:** based on supportive findings from fair-quality studies or mixed findings with most favouring one conclusion, or no firm conclusions e) **None or Insufficient:** based on mixed findings, a single poor study, or the endpoint has not been studied, with substantial uncertainty attributable to chance, bias, and confounding factors" (e3)

Characteristics of the Guideline	
Study Population(s)	• Cannabis users, with certain information regarding special-risk populations
Exposure	• Cannabis use (including various behavioural characteristics related to use)
Outcome(s)	• Alterations in brain structure • Functional connectivity • IQ • Cognitive and executive functioning • Behavioral impulsivity • Dependence • Motor vehicle accident • Attention • Verbal learning and memory • Impulse control • Depressive symptoms • Psychotic symptoms • Early school leaving • Postsecondary degree noncompletion • Other substance use, alcohol and illegal drug dependence • High-school and university degree attainment • Other substance use • Alcohol and illegal drug dependence • Paranoia • Pulmonary or bronchial problems (e.g., coughing, excessive sputum, wheezing, shortness of breath) • Acute bronchitis • Impaired respiratory functioning • Emphysematous lung bullae • Lung cancer • Intake of hazardous byproducts, tar, particulate matter • Infectious disease transmission • Hydrocarbon burns • Impairment • Tolerance • Withdrawal symptoms • Poisonings • Cardiovascular problems

	• Mania • Suicide • Anxiety disorder • Socioeconomic outcomes • Psychomotor functioning • Anemia • Fetal growth reduction and decreased birth weight (as it relates to pregnancy) • Placement in neonatal care units (as it relates to pregnancy) • Child development and behaviour problems (as it relates to maternal cannabis use) • School performance (as it relates to maternal cannabis use)
Results of the Review	

Relevant Review Results	**Early Use Initiation**
	• **There is substantial evidence that "early initiation of cannabis use (i.e., most clearly that which begins before age 16) is associated with multiple subsequent adverse health and social effects in young adult life. These effects are particularly pronounced in early-onset users who also engage in intensive/frequent use. This may be in part because frequent cannabis use affects the developing brain."** (e4)
	• "Early-onset cannabis users have shown alterations of white and gray brain matter and cortical thickness; lowered functional connectivity, IQ, and cognitive functioning; and greater behavioral impulsivity." (e3)
	• Compared with later onset users, earlier onset users:
	  ○ "Commonly used cannabis more intensively" (e3)
	  ○ "Subsequently showed poorer cognitive and executive functioning" (e3)
	  ○ Have nearly double the risk of cannabis dependence (1 in 6 versus 1 in 10, respectively) as shown in one study. In another study, they are 4 times more likely to develop dependence.
	  ○ Are 3 times more likely to have a motor vehicle accident
	• "Among cannabis-dependent users, early onset is associated with:
	  ○ Subsequent poorer attention
	  ○ Verbal learning and memory
	  ○ Impulse control
	  ○ Executive functioning outcomes" (e3)
	• "Early onset use is associated with an elevated risk for developing mental health problems, including depressive symptoms and psychotic symptoms" (e3)
	• "No associations were found between cannabis use and psychosis or reduced IQ among those initiating use after age 18 years." (e3)
	• In a longitudinal sibling-pair study, an increased risk was observed among those initiating use before age 16 for the outcomes listed below (the association persisted when examined in sibling pairs):
	  ○ Nonaffective psychosis (OR 2.2, 95% CI=1.1 to 4.5)
	  ○ Delusions (OR 4.2, 95% CI=4.2 to 5.8)

- Experiencing hallucinations (OR 2.8, 95% CI=1.9 to 4.1)
- "In a subsample of male twins discordant for cannabis use, early-onset users had elevated risk of subsequent other substance use, and for alcohol and illegal drug dependence, compared with controls" (e3)
- "In a meta-analysis of longitudinal studies, never-users of cannabis by age 18 years had greater odds of high-school and university degree attainment, compared with those who started use before age 15 years" (e3)
- "Other studies demonstrated poorer educational outcomes, including a risk of early school leaving or postsecondary degree noncompletion" (e3)

Cannabis Products

- **There is substantial evidence that "high THC-content products are generally associated with higher risks for various (acute and chronic) mental and behavioural problem outcomes."** (e4)
- "Frequent use of high-potency cannabis ("skunk") has been associated with:
  - Marked effects on memory
  - Increased paranoia
  - Greater dependence severity in (especially younger) users in the UK" (e3, e5)
- "Use of high-potency "wax dabs" has been linked to cannabis-induced psychosis among individuals with no psychiatric history" (e5)

Cannabis Use Practices

- **Overall, there is substantial evidence that "regular inhalation of combusted cannabis adversely affects respiratory health outcomes"** (e4)
  - **Alternative delivery methods come with their own risks but are preferable to routes of administrate that involve smoking combusted cannabis material** (**Note:** On e7, the authors note that the evidence is weaker for the use of alternative delivery methods due to absence of rigorous studies)
  - **"Use of edibles eliminates respiratory risks, but the delayed onset of psychoactive effect may result in use of larger than intended doses and subsequently increased (mainly acute, e.g., from impairment) adverse effects"** (e4)
- **There is limited evidence that "practices such "deep inhalation,' breath-holding,' or the Valsalva maneuver to increase the intake of toxic material into the pulmonary system…disproportionately increases the intake of toxic material into the pulmonary system."** (e4)
- Systematic reviews and major studies have found that cannabis smoking is associated with:
  - "Various pulmonary or bronchial problems (e.g., coughing, excessive sputum, wheezing, shortness of breath)" (e5)
  - Acute bronchitis
  - Impaired respiratory functioning
- Many of these problems appear to be associated with use intensity. However, they may be reversible following cessation.
- "Emphysematous lung bullae have been detected among young cannabis smokers" (e5)
- "There is mixed evidence for associations of cannabis smoking with lung cancer, with only some studies reporting associations; among those showing associations, the risk is moderately elevated (1.5- to 4-fold) and associations continue to be inconclusive

mainly because of confounding by tobacco use" (e5)

- "Breath-holding or deep inhalation practices (intended to intensify the absorption of psychoactive components) increase the intake of hazardous byproducts (e.g., carcinogens, tar and other toxins, carbon monoxide)" (e5)
- "Bongs or water pipes may reduce burnt particle inhalation while increasing tar or particulate matter intake" (e5) as well as infectious disease (e.g., pulmonary tuberculosis)
- "Vaporizer devices eliminate cannabis combustion and thus reduce toxic compound intake and related pulmonary problems" (e5)
    - "In 2 experimental studies, respiratory problems (including bronchitis) significantly improved among users switching to vaporizer use, but the lag in onset of psychoactive effects led to higher dosing" (e5)
    - "No rigorous studies exist on the long-term effects of vaporizer use" (e5)
- "For cannabis e-cigarette devices, formaldehyde particles have been detected at higher voltage that may expose users to risky toxins" (e5)
- "Dabbing (the inhaling of flash-vaporized cannabis concentrates) has been associated with elevated risks of hydrocarbon burns and inhalation of solder, rust, and benzene, in addition to greater impairment, tolerance, and withdrawal symptoms" (e5)
- There are acute risks with edible products including the delayed onset of psychoactive effects which may lead to potential overconsumption. This potentially contributes to increases in poisonings and hospitalizations where these products are available (e.g., Colorado).
- "Edible cannabis products can also be accidentally ingested by children who then require treatment" (e5)

Frequency of use

- **There is substantial evidence that "frequent or intensive (e.g., daily or near-daily) cannabis use is strongly associated with higher risks of experiencing adverse health and social outcomes related to cannabis use"** (e4)
    - **"There is less evidence on outcomes if frequency/intensity of use decreases, but the general principle of a dose-response based potential for effect reversal should be assumed, as it has been shown for other psychoactive substances"** (extended evidence grade supplement, pg 3)
- "Systematic reviews have found associations between the frequency or intensity of cannabis use and various adverse health outcomes, including mental health problems, cardiovascular problems, MVAs, suicidality, changes in brain structure, and neurocognitive effects" (e6)
    - "Morphological brain alterations have been observed in both adolescents and adults" (e6)
    - "In case-control studies, use intensity has an inverse association with brain volume and structure integrity." (e6)
    - "The magnitude of brain abnormalities and the persistence of acute impairment of executive functions (e.g., cognition, memory, psychomotor control) may be influenced by intensity" (e6)
    - "There is evidence for tolerance effects resulting in reduced cognitive impairment among frequent or chronic users" (e6)
- There are similar findings in individual studies related to mental health and other outcomes:
    - "Studies from various countries have identified cannabis use frequency as a predictor of psychosis, depressive symptoms, mania, and suicide" (e6)

- "In a longitudinal cohort, daily cannabis use was associated with anxiety disorder (OR 2.5, 95% CI=1.2 to 5.2) and cannabis dependence (OR 2.2, 95% CI=1.1 to 4.4); those with persistent daily cannabis use at age 29 years remained at elevated odds for anxiety disorder (OR 3.2, 95% CI=1.1 to 9.2)" (e6)
- "The risk of cannabis dependence was 5-fold among daily versus infrequent users in Australia" (e6)
- "Frequent use predicted dependence severity among adult users in the United Kingdom" (e5)
- "An exception may be a Dutch study in which use frequency was not associated with incidence of dependence; however, this study involved frequent and age-limited users only" (e6)

- Other studies demonstrated poorer educational outcomes, including a risk of early school leaving or postsecondary degree noncompletion
  - "Similar associations with educational, socioeconomic, and other substance use outcomes have been shown" in other studies (e6)
- "Several studies have found that MVA risk is increased among frequent users" (e6)
- "Use frequency also predicted higher overall and specific problem domain outcomes on the Alcohol, Smoking, and Substance Involvement Screening Test; daily or near-daily users were at least 9 times more likely to experience problems than infrequent users" (e6)

Cannabis Use and Driving

- **There is substantial evidence that "driving while impaired from cannabis is associated with an increased risk of involvement in motor-vehicle accidents".** (e4)
  - **"The use of both cannabis and alcohol results in multiply increased impairment and risks for driving, and categorically should be avoided"** (e4)
- "Cannabis use acutely impairs key executive functions critical for driving, including cognition, attention, memory, decision-making, and psychomotor functioning" (e6)
  - "This occurs in a dose-dependent way, although the magnitude and persistence of impairments may vary with use patterns, THC concentration, tolerance, metabolism, and other factors" (e6)
  - "Some of these impairments have been found to persist after acute intoxication, particularly in chronic users" (e6)
- "Higher THC or other cannabinoid concentration or ingested cannabis products (with an extended absorption period) can have more pronounced and persistent effects" (e6) on intoxication and cognitive impairments
  - These effects also vary on THC pharmacokinetics, inhalation intensity, lung capacity, and other factors
- "Epidemiological studies have clearly established that acute cannabis impairment increases the risk of MVA involvement, including fata collisions (a notable exception: National Highway Traffic Safety Administration)" (e6)
- "Several meta-analyses and reviews concluded that there is an approximate 1.3- to 3-fold (low-to-medium magnitude) increase in MVA risk after cannabis use" (e6)
  - "A recent Canadian case-crossover study found cannabis use to be associated with a 4-fold increase in MVA involvement. Risk of MVA involvement increases in a dose-related way with THC concentration or frequency of cannabis use" (e6)
  - "This risk is substantially higher when cannabis and alcohol use are combined" (e6)

	Special Risk Populations
	• **There is substantial evidence that "there are some populations at probable higher risk for cannabis-related adverse effects who should refrain from using cannabis. These include: individuals with predisposition for, or a first-degree family history of psychosis and substance use disorders, as well as pregnant women"** (e4)
	• "Several studies have concluded that a substantial proportion of cannabis-attributable psychosis occurs among users with a family or personal history of psychosis, and a genetic predisposition to psychosis may be triggered or amplified by cannabis use" (e6)
	  ○ "Assuming that risk of psychosis from family history and cannabis use are multiplicative, someone with a first-degree relative with a history of psychosis has a 10% baseline risk, which is doubled if they become regular users" (e6)
	  ○ "It is unclear whether such dynamics also exist for other mental health risks, such as depression, anxiety, or suicide, for which associations with cannabis have been shown (e6)
	• "A systematic review found that women who used cannabis during pregnancy had increased odds of anemia (pOR 1.4, 95% CI=1.1 to 1.7), decreased birth weight (pOR=1.8, 95% CI 1.3 to 3.0), and placement in neonatal care units (pOR=2.0; 95% CI=1.3 to 3.2) (e7)
	• "Maternal cannabis use has been associated with fetal growth reduction and decreased birth weight in newborns, as well as with child development and behaviour problems, poor school performance, and illicit drug use in children" (e7)
	• "Case-control studies have found associations for different cancers among children when maternal cannabis use occurred during pregnancy, but provide weak evidence for causal associations" (e7)

Limitations	• None specifically identified by the authors, however, it is noted that "most studies reviewed were cross-sectional and naturalistic, implying caution with causal interpretations and conclusions about the magnitudes of effects" (e3)

Evidence brief: Health effects of cannabis exposure in pregnancy and breastfeeding	
General Information and Quality Rating	
Type of Article	Review of reviews
Author(s) and Date	Ontario Agency for Health Protection and Promotion (Public Health Ontario), Carsley S, Leece P (November 2018)
Country	Canada
Quality Rating	8/10 (Using Health Evidence™ Quality Assessment Tool)
Details of the Review	
Objective(s)	The evidence brief addresses two questions (Note: only the first question is relevant to the FPQ): 1. What are the child and youth outcomes associated with exposure to maternal cannabis use during preconception, pregnancy or breastfeeding? 2. What are the current clinical recommendations for providers caring for reproductive-age, pregnant or breastfeeding women who may use cannabis?
Database(s) Searched	• Ovid MEDLINE, Embase, PsychINFO, CINAHL • Grey literature: general web searches of .org and .gov, custom search engine for/of Canadian public health information, international organizations, and government agencies
Search Period	• 2006 to April 2018
Inclusion/Exclusion Criteria	Inclusion criteria: • Systematic reviews • English language • Human studies • Reported on "the effects of cannabis exposure on offspring through maternal use during preconception, pregnancy, infancy or childhood" (pg. 4) (although the review also reported on maternal outcomes) • Focused on any health, developmental or social outcomes • With respect to guidelines, used a structured approach to reviewing scientific literature and transparent method for generating evidence-based recommendations Exclusion criteria: • None stated
Number and Type(s) of Articles Included	• 11 articles: ○ 6 systematic reviews, 3 with meta-analyses ○ 5 guidelines Note: only the systematic reviews are relevant to the FPQ.
Article	• Not applicable

Prioritization During Relevance Screening	

Quality Appraisal Process and Results	• Quality of included articles was conducted by two reviewers using:
	  ○ The Health Evidence™ Quality Assessment Tool for systematic reviews
	  ○ The Agree II Guideline Appraisal Tool for clinical practice guidelines
	• Four systematic reviews were rated as 'strong', two were rated as 'moderate' (Note: only the quality of articles relevant to the FPQ are reported)

Strength of Evidence Assessment	• Not applicable
Characteristics of the Review	
Study Population(s)	• Offspring (infants, children and youth) of mothers who used cannabis during pregnancy and breastfeeding periods • Pregnant women
Exposure(s)	• Cannabis use during pregnancy, as determined by self-report (2 reviews) • Cannabis use during pregnancy, as determined by both self-report and objective measures (1 review) • Cannabis use while breastfeeding (Note: method of exposure assessment not stated) (3 reviews)

Outcome(s)	**1. Outcomes related to cannabis use during pregnancy** (Note: There were additional outcomes listed within the data extraction table of the evidence brief. However, these are not captured below as they were not included within the main body of the evidence brief)
	<u>Infant/children/youth outcomes</u>
	• Fetal growth and development
	  ○ low birth weight (< 2500g) (2 reviews)
	  ○ birth weight (2 reviews)
	  ○ head circumference (1 review)
	  ○ neonatal length (1 review)
	• Neonatal
	  ○ NICU admission/level II or greater nursery admission (2 reviews)
	  ○ preterm delivery (<37 weeks) (2 reviews)
	  ○ gestational age (2 reviews)
	  ○ Apgar score (1 review)
	  ○
	• Pregnancy complications
	  ○ still birth (1 review)

	○ spontaneous abortion (1 review) ○ placental abruption (1 review) ○ perinatal death (1 review) • Conduct problems (1 review) <u>Maternal outcomes</u> • anaemia (1 review) **2. Outcomes related to cannabis use during breastfeeding** <u>Infant/children/youth outcomes</u> • SIDS (3 reviews) • Mental and motor development at one year (2 reviews) • Infant physical growth (1 review)
Results of the Review	
Relevant Review Results	**1. Results Related to Cannabis Use During Pregnancy** **Fetal Growth and Development** • Low birth weight and birth weight ○ One meta-analysis (strong quality) found cannabis use during pregnancy increased the risk for low infant birth weight (RR: 1.43, 95% CI 1.27 to 0.62). This estimate became statistically insignificant after controlling for confounders (i.e., tobacco use and other substances, socioeconomic and demographic factors). (p.5) ▪ Evidence brief authors noted that given the small sample sizes of the included studies, the meta-analysis was likely underpowered to detect significant differences. ○ The second meta-analysis (strong quality) found cannabis use during pregnancy is associated with a significant reduction in birth weight of 109.42 g (95% CI 38.72 to 180.12) and higher odds of low birth weight (<2500g) (pOR: 1.77, 95%CI 1.07 to 3.01) (did not control for poly-substance use). (p.5) • Head circumference and neonatal length ○ One meta-analysis (strong quality) mentioned head circumference and neonatal length as outcomes in discussion; however, no results were given. **Neonatal Outcomes** • NICU admission ○ One meta-analysis (strong quality) found cannabis use during pregnancy increased odds of NICU admission (pOR: 2.02, 95% CI 1.27 to 3.21) (did not control for poly-substance use). (p.5)

- The second meta-analysis (strong quality) mentioned level II or greater nursery admission as an outcome in discussion; however, no result was given.

- Preterm delivery
  - One meta-analysis (strong quality) found cannabis use during pregnancy increased the risk for preterm delivery (RR: 1.32, 95% CI 1.14 to 1.54). This estimate became statistically insignificant after controlling for confounders (i.e., tobacco use and other substances, socioeconomic and demographic factors). (p.5)
    - Evidence brief authors noted that given the small sample sizes of the included studies, the meta-analysis was likely underpowered to detect significant differences.
  - The second meta-analysis (strong quality) mentioned preterm birth as an outcome in discussion; however, no result was given.
  - The second meta-analysis (strong quality) found no significant association between cannabis use in pregnancy and preterm birth (did not control for poly-substance use) (Note: no effect size given).
- Gestational age and Apgar score
  - Two meta-analyses (both strong quality) mentioned gestational age as an outcome in discussion; however, no result was given.
  - One meta-analysis (strong quality) mentioned Apgar score as an outcome in discussion, however, no result was given.

Pregnancy Complications

- Still birth, spontaneous abortion, placental abruption and perinatal death
  - One meta-analysis (strong quality) mentioned still birth, spontaneous abortion, placental abruption, and perinatal death as outcomes in discussion, however, no results were given.

Conduct Problems

- One meta-analysis (strong quality) found no significant association between cannabis use in pregnancy and conduct problems in children or youth (pOR: 1.29, 95% CI 0.93 to 1.81). (p. 6)
  - The evidence brief authors noted the quality assessment of the three included studies was 'low to very low' and the review authors determined there were insufficient studies to draw conclusions for this association.

Maternal Outcomes

- Anemia
  - One meta-analysis (strong quality) showed a significant increase in odds of anaemia compared to those who did not use cannabis (pOR: 1.36, 95% CI 1.10 to 1.69) (did not control for poly-substance use). (p. 6)

2. Results Related to Cannabis Use During Breastfeeding

- There was no significant association found between cannabis use during breastfeeding and any health outcomes in humans or

	animals (three systematic reviews, one strong and two moderate quality) (Note: no effect size given). ○ The evidence brief authors noted the primary studies included in all three reviews were limited in number, dated and had overlap between reviews.
Limitations	**Limitations of the Included Reviews (as noted by the evidence brief authors)** <u>Lack of Human Epidemiologic Studies</u> • In three systematic reviews, the primary studies were largely from three longitudinal cohort studies; two of which started in the 1980s. ○ Potency of cannabis has substantially increased since this time, so studies based on past use may not be applicable to current use. ○ These cohorts had relatively small sample sizes, specific populations and looked at different outcomes, increasing heterogeneity of studies in the meta-analysis. <u>Poor Control of Concurrent Exposures and Other Confounders</u> • Most included studies within the reviews were unable to control for confounders: ○ The conclusions of two meta-analyses were conflicting; one meta-analysis indicated no independent risk of cannabis on neonatal outcomes, while the second review reported overall adverse effects of cannabis use during pregnancy. The former meta-analyses did control for poly-substance use, especially tobacco, whereas the latter did not. ○ Studies within the three systematic reviews focused on cannabis use during lactation were unable to control for maternal cannabis use in the first trimester of pregnancy. <u>Measurement of Cannabis Exposure</u> • Self-reporting cannabis use is the most common method for measuring exposure; yet, social desirability and reporting biases likely underestimate use. **Limitations of the Evidence Brief (as noted by the evidence brief authors)** • Authors did not search for the effect of cannabis use on parenting, parent-child attachment, which may affect latent child health outcomes. • Authors focused on literature published since 2006 • Authors did not include primary studies or systematic reviews reported only in the grey literature