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Cannabis-Related Health Effects: An Updated Overview

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Abbreviations

Table 1. List of Abbreviations

2SLGBTQ+	Two-Spirit, Lesbian, Gay, Bisexual, Transgender, Queer or Questioning
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
CBD	Cannabidiol
CI	Confidence interval
HIV	Human immunodeficiency virus
HTA	Health Technology Assessment
IQ	Intelligence quotient
MA	Meta-analysis
OR	Odds ratio
QA	Quality Assessment
QoL	Quality of Life
SR	Systematic Review
THC	Tetrahydrocannabinol
UK	United Kingdom
USA	United States

1. Executive Summary

Scientific literature was searched for systematic reviews that explored the association between cannabis use and health effects. Findings from the included reviews were categorized into the following results categories: results from meta-analyses were categorized as "harm", "benefit", or "no significant evidence of association"; results from systematic reviews that *did not report pooled analyses* were categorized as "inconclusive" (Box 1).

Box 1: Categorization of Findings

Harm: pooled analysis reported a significant association between cannabis use and harmful health outcome

Benefit: pooled analysis reported a significant association between cannabis use and beneficial health outcome

No significant evidence of association: pooled analysis reported no statistically significant association between cannabis use and health outcome. This is also referred to as **non-significant association.**

Inconclusive: Results from systematic reviews without a meta-analysis are unable to estimate the overall measure of effect of cannabis on a health outcome. For this reason, systematic reviews are not weighted the same as a meta-analysis, and could not be categorized in the same way. Therefore, systematic reviews were categorized as inconclusive.

Ninety-nine systematic reviews were included, reporting a total of 66 different health outcomes across the following six health domains: overall health effects, mental health effects, cancer, changes to the brain, neurocognition, and prenatal exposure. Mental health effects and overall health effects were reported most often, followed by neurocognition and changes to the brain.

Even with this rapidly accumulating evidence, there are few definitive conclusions that can be drawn about the impact of cannabis on health outcomes. For mental health effects, only two outcomes reported consistent findings. For bipolar disorder and depression, all meta-analyses reported a harmful association with cannabis use. For general psychiatric symptoms, schizophrenia, and suicidality, a combination of inconclusive and harmful associations were reported. For anxiety and psychosis, a combination of no significant evidence, inconclusive, and harmful associations were reported. Taken together, these findings continue to support the recommendations that people experiencing mental illnesses should abstain from cannabis use.

For cancer, there were no pooled analyses to support an association between cannabis use and any of the included cancers, except for testicular, and head and neck cancer. A pooled analysis of an association between cannabis use and testicular cancer was conducted in seven systematic reviews, of which five reported a harmful association, and two reported non-significant associations. Head and neck cancer reported two pooled analyses, of which both reported non-significant associations. For the other cancers, the literature is limited to systematic reviews only, therefore, categorized as inconclusive. The current body of literature does not support a conclusion on whether or not cannabis use is harmful for other cancers.

For respiratory symptoms including wheezing, coughing, dyspnea, and sputum production, there were six associations investigated by meta-analysis; four of which reported a harmful association, and two reported non-significant associations. At this time it is not clear whether these harmful associations are a result of the cannabis substance, the inhalation of it, or a combination of both, highlighting the need for future research. Overall, these findings support recommendations that people with existing respiratory conditions should abstain from inhaling cannabis.

The findings on the impact of cannabis use on neurocognition are mixed. For the outcomes of attention, cognitive function, executive function, learning, and memory, multiple meta-analyses found a total of 24 harmful associations, and 13 non-significant associations. An additional 23 systematic reviews did not conduct meta-analysis and were therefore categorized as inconclusive. As a result of these mixed findings, no conclusions can be drawn on whether or not cannabis use is harmful for neurocognition for the general population. However, when exploring the systematic reviews on adolescents and young adults only, the evidence is more consistent. In adolescents and young adults, there is evidence of harm for cannabis use and attention, memory, learning, executive function, and overall neurocognition. Given his body of literature, it seems prudent to continue to recommend that people under the age of 18 should abstain from cannabis use.

Prenatal exposure describes the effects of cannabis use during fetal development in-utero. Harmful associations exist between cannabis use and birth weight, gestational age at birth, maternal outcomes (e.g., anemia), and neonatal placement in the ICU, however, the evidence is limited. Inconclusive results were reported for pre/postnatal effects including adverse obstetrical outcomes, childhood cognitive function, childhood mental health, fetal neurobehavioural effects, perinatal death, and placental abruption. Given the limitations in the literature, recommendations that cannabis should not be used during pregnancy should continue to be reinforced.

Even with the abundance of cannabis-related literature, gaps still exist. No reviews that explored cannabis use on specific populations such as ethnic minorities, Indigenous people, or 2SLGBTQ+ populations were identified. Additionally, few studies considered age or sex in reporting the health effects of cannabis use. Much of the evidence reported from the included reviews relies on primary studies that do not permit an understanding of the direction of association between cannabis use and health outcomes (e.g., case-control and cross-sectional data). Pooled analyses of longitudinal studies, or randomized control trials, will provide a better understanding of the direction of association between cannabis use and health effects.

There are some notable limitations to this overview. Medicinal use of cannabis was not considered, therefore possible therapeutic or medical effects of cannabis were not captured. The term “cannabis use” is defined in multiple ways in the included literature, therefore we were unable to provide conclusions on how dose, frequency, type of cannabis and mode of use (e.g., edible, inhalation) affects health outcomes differently. Lastly, pooled estimates are not reported for many of the health outcomes explored in this review. For this reason, we are unable to determine the effect size, if any, that cannabis use may have on these health outcomes.

Despite extensive interest in cannabis-related research, there are few or mixed findings from published meta-analyses. Based on the evidence herein, it is reasonable to conclude that those experiencing mental illnesses, those with existing respiratory conditions, people under the age of 18 years, and women who are pregnant should abstain from using cannabis. More evidence, particularly high-quality meta-analyses on longitudinal studies or randomized controlled trials, is required to understand the causal effect of cannabis on other aspects of health. As interest in the

health effects of cannabis continue to rise and more studies emerge, more conclusive evidence may become available in the coming years.

2. Background

Cannabis sativa, also known as cannabis, marijuana, weed, maryjane, pot, or bud, is a multi-use crop that has been cultivated by humans for thousands of years. "Cannabis" generally refers to the plant as a whole, while "marijuana" (pot) refers to the dried leaves of the cannabis plant.[1] Today, there are three varieties of cannabis, *C. sativa*, *C. indica*, and 'hybrid strains', each of which induce different physiological and psychological effects depending on cannabinoid profiles.[2] There are at least 70 naturally occurring cannabinoids in cannabis,[3] although the two most referenced cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD). In addition to interacting with each other, these cannabinoids may also be affected by the concentration and route of administration, for example, through combustion.

Medicinal cannabinoids, such as nabilone, are structurally related to naturally occurring cannabinoids like THC, and selected for biological potency.[4] Synthetic cannabinoids, such as "Spice," "K2," and "Kronic" differ structurally from THC or CBD, however, users report similar effects to non-synthetic cannabis.[5] Cannabis concentrates such as "wax" or "shatter", refer to cannabinoids from raw plant forms of cannabis, with increased potency, concentration, and a variety of methods of consumption.

In Canada, cannabis has been legally authorized for medical use, colloquially known as medical marijuana, since 2001. In 2015, the Government of Canada announced plans to legalize cannabis for non-medical use and in June of 2016, a nine-member federal task force on cannabis, chaired by Hon. Anne McLellan, was established. Guided by this task force, Canada became the second country to legalize non-medical cannabis use under the Cannabis Act, Bill C-45 on October 17, 2018.[6]

The Cannabis Act sets regulations at the federal level to control the production, distribution, sale, and possession of cannabis.[7] This includes two primary measures to protect youth, including age restrictions – legal possession of 30 grams dried cannabis or equivalent for people over the age

of 18 years (note: this is increased to drinking age in some provinces/territories); and restricting promotion and enticement – prohibiting product labelling that appears to youth, self-service displays of vending machines, promoting cannabis products.[7] The federal and provincial or territorial governments are responsible for the regulation of cannabis. On a federal level, the government is responsible for enforcing requirements and regulations for producers who grow and manufacture cannabis, including: type of product for sale (e.g., dried leaves, oil, etc.) packaging and labelling, serving sizes and potency, and prohibition of certain ingredients.[7]

On a provincial or territorial level, the governments are responsible for developing, implementing, maintaining, and enforcing systems to oversee cannabis distribution.[7] Additionally, each province or territory can develop their own regulations, such as increasing the legal age of consumption, decreasing the legal amount for personal possession, and restricting where adults may consume cannabis.[7] Alberta adopted the maximum amount of non-medical cannabis allowed for public possession, which is 30 grams of dried cannabis, or equivalent in non-dried form. In terms of taxation, federal flat-rates and additional flat-rate cannabis duties are imposed on the input included in the cannabis product (i.e. flower, trim, seed, and seedling). Alberta applies an additional sales tax adjustment rate which applies to the additional cannabis rates,[8] along with the respective applicable GST.

A 2020 report by *Statistics Canada* reported that after legalization of cannabis, nearly 17% of Canadians reported "any cannabis use in the previous three months", compared to nearly 15% prior to legalization. [9] The highest prevalence of use observed among those between the ages of 18 and 24 (33.3%).[9] Additionally, a higher prevalence of males (20.3%) reported cannabis use in the previous three months compared to females (13.4%).[9] Prior to legalization, 11% of cannabis users reported accessing cannabis through legal means only; after legalization, this number increased to nearly 30%.[9] In 2019, the most common method of cannabis consumption was smoking (84%), with other common methods of consumption including: eating it in food (46%), vaporizing using a vape pen or e-cigarette (27%), and vaporizing using a vaporizer (15%).[10] The most common cannabis products used by Canadians were: dried flower/leaf (77%), edible food products (44%), vape pens/cartridges (26%), hashish/kief (23%), cannabis oil for oral use (23%), and concentrates/extracts (17%).[10]

The selected route of administration affects the speed of onset, duration, intensity of effects, and side effect profile.[11] Although clearly differentiated above, "cannabis" in the vernacular has a wide scope of usage and can refer to any of the above compounds and methods of administration.

To inform Alberta's response to the federal decision to legalize cannabis, the University of Calgary's Health Technology Assessment (HTA) Unit was commissioned to complete an evidence synthesis in 2016 to support the policy development of the Government of Alberta.[12] This evidence synthesis involved five chapters: current Canadian context, health harms and effects, medical cannabis, advertising and communication and experience with legalization economic, sales and use regulations. To continue to support evidence-informed policy development and research in Alberta, the University of Calgary's HTA Unit was asked to update the review of the health harms and effects of non-medical cannabis use.

3. Methods

3.1. Data Sources and Searches

In the original HTA Unit report, six databases were searched from inception until May 2016: Medline, the Cochrane database of Systematic Reviews, EMBASE, PsycINFO, CINAHL, and the HTA database. The search strategy was developed by a medical librarian. In this update, the search was updated from May 2016 to July 9th, 2020 using the same databases and search strategy to inform this updated overview. Terms for marijuana, such as cannabis, marihuana, pot, or weed were combined with terms for adverse health effects, such as adverse event, harm, or reaction, change, and impairment. The search was limited to English or French, systematic reviews and meta-analyses. The full search strategy can be found in *Appendix 1: Search Strategy*.

3.2. Study Selection

All abstracts were screened by two independent reviewers. For inclusion, citations needed to meet the following criteria: systematic review design (i.e., described by author as a systematic review, and searched more than one database); published in English or French; focused on human populations; reported on non-medical cannabis use; and reported a health effect or harm (Table 2). Given the substantial increase in cannabis-related reviews since 2016, a modified inclusion criteria was carried out in the updated search. For example, there were added criteria for what was considered a systematic review in the updated search (e.g., only included primary studies). Additionally, behaviour-related outcomes such as relapse and motor vehicle collisions, and cross-interaction with other drugs were excluded.

To ensure all relevant literature was captured, abstracts included by either reviewer proceeded to full-text review. All full texts were reviewed in duplicate by two reviewers. Any discrepancies between reviewers were resolved through discussion and consensus. All identified full-texts were hand searched to ensure no relevant literature was missed in the database search.

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria

• Human population
• Assesses at least one of the following:
  ○ Acute and chronic health effects related to cannabis use
  ○ Addictiveness of cannabis
  ○ Cannabis dependence
  ○ Safety of cannabis use for the general population or for special populations (e.g. pregnant women, youth)
  ○ Health effects, harms and safety of drug delivery modes
• Systematic review design (defined by author as a systematic review, ≥2 databases searched, only included primary studies)
	• Any study design other than a systematic review
	• Did not report any health effects of interest (e.g., social or behavioural outcomes)
	• Does not examine impact on humans
	• Not written in English or French
	• Includes synthetic cannabis only
	• Medicinal/therapeutic cannabis
	• Reviews that include multiple substances (e.g., cannabis combined with other substances)

3.3. Data Extraction, Quality Assessment, and Analysis

For all included reviews, data on author, year and country of publication, search strategy, number of papers included, patient characteristics and key outcomes were extracted. Quality was assessed using the AMSTAR checklist.[13] Items covered by AMSTAR include the presence of a priori design, duplicate selection and data extraction, a list of included and excluded studies, and whether the status of publication was used as inclusion criteria, the quality of included studies and likelihood of publication bias was assessed, and the mode of combining the studies was appropriate.[13] All studies were given a final score out of eleven. Studies with a score of 0-4 were considered low quality, scores of 5-8 were considered moderate quality, and scores of 9-11 were considered high quality.[14]

Evidence was grouped into six categories of health effects:

- *overall health effects* including outcomes such as overall mortality, overall health, and cardiovascular health;
- *mental health effects* including psychosis, schizophrenia, anxiety, and suicide;
- *cancer* of all types;
- *changes to the brain* including structural (e.g., changes in physical structure of the brain

including development and brain volume), functional (e.g., changes in brain activity and function including blood flow and brain activation), and chemical (e.g., changes in neurotransmitter levels including dopamine and glutamate) changes within the brain;
- *neurocognitive effects* such as learning, memory, and psychomotor functioning; and,
- *prenatal exposure* including birth weight and birth complications.

Meta-analyses are the gold standard for synthesizing primary studies. Unlike a systematic review, which often relies on narrative synthesis of the included studies and does not provide a quantitative summary of effects (e.g., pooled analysis), a meta-analysis summarizes the results of all relevant studies and estimates an average effect across all studies.[15] As such, there is a growing reliance on meta-analytic data for decision making and policy development. For the purpose of this updated overview, findings from the included reviews were categorized into four findings categories based on whether the results were reported from a meta-analysis, or from a systematic review with a narrative synthesis. Given the considerable increase in meta-analyses reported after 2016, and in order to present consistent findings between the reviews reported in the original report, and those captured in the updated search, findings reported for reviews from the original report were also assessed through this analytic frame. A detailed comparison of the included studies within the original HTA Unit report can be found in *Appendix 2: Supplementary Tables and Figures*.

Results from meta-analyses were categorized as:

- "harm" (pooled analysis reported a significant association between cannabis use and harmful health outcome),
- "benefit" (pooled analysis reported a significant association between cannabis use and beneficial health outcome), or
- "no significant evidence of association", or "non-significant association" (pooled analysis reported no statistically significant association between cannabis use and health outcome).

Results from systematic reviews that *did not report pooled analyses (e.g., meta-analysis)* were categorized as "inconclusive". Inconclusive findings indicate that evidence exists, however,

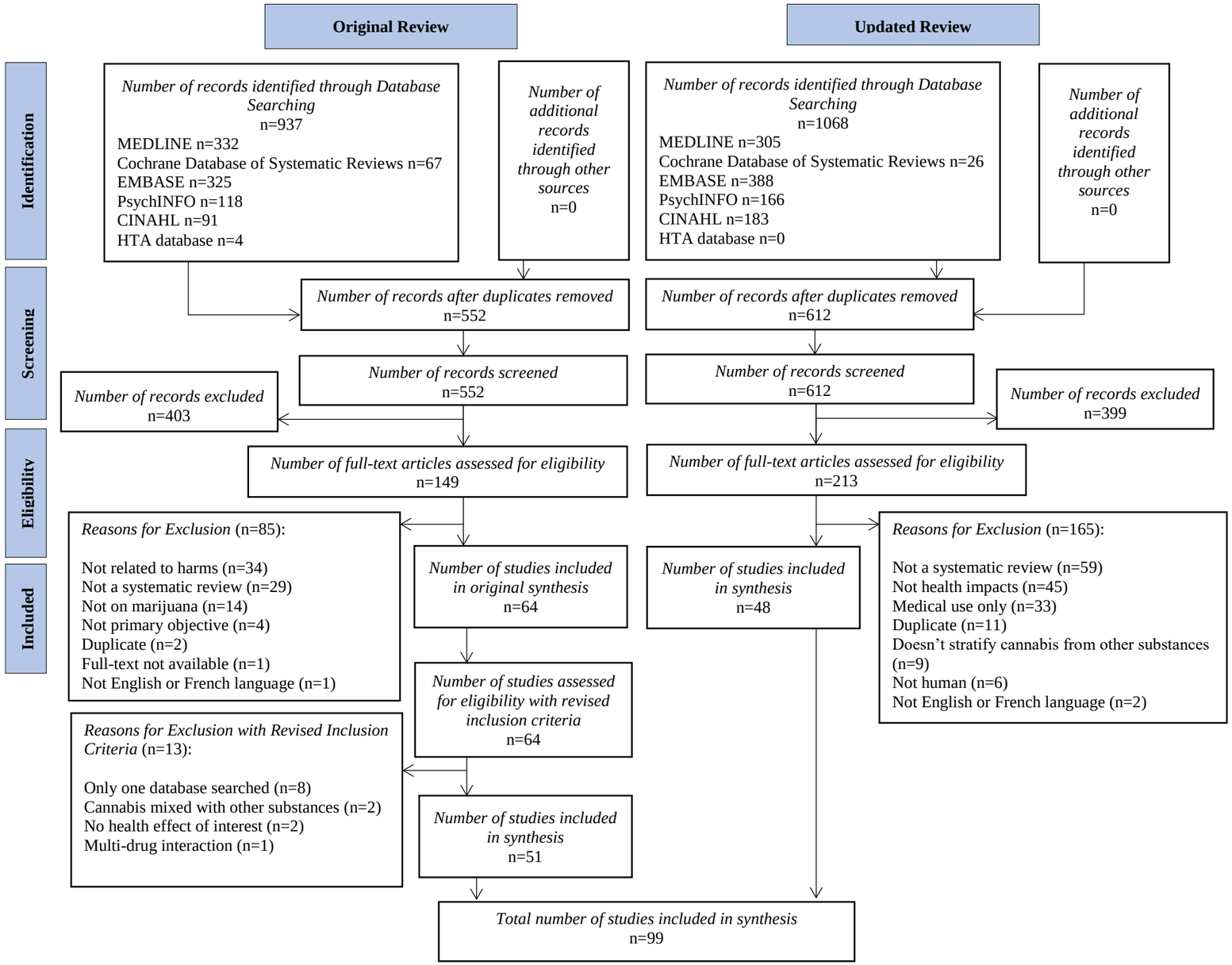
without a pooled estimate, the overall effect size (e.g., strength of association), between cannabis use and the health outcome of interest remains unknown. The term “mixed results” is used to indicate that for a single health outcome, there were multiple systematic reviews with a combination of findings (e.g., harm and/or benefit and/or no significant evidence of association and/or inconclusive).

4. Results

In the original report including reviews from inception to May 2016, 552 unique abstracts were retrieved and reviewed, with 149 proceeding to full-text review (Figure 1). In the updated search from May 2016 to July 2020, 612 unique abstracts were retrieved and reviewed, with 213 proceeding to full-text review. This indicates the rapid increase in cannabis related research from 2016 to 2020. Sixty-four systematic reviews were included in the original overview. Based on the updated inclusion criteria for this updated overview, 13 of these systematic reviews were excluded in the final dataset reported in this overview. Reasons for exclusion included: only one database searched (n=8); cannabis mixed with other substances (n=2); health effect not of interest (n=2); and multi-drug interaction (n=1). Fifty-one systematic reviews from the original overview were included in this update.

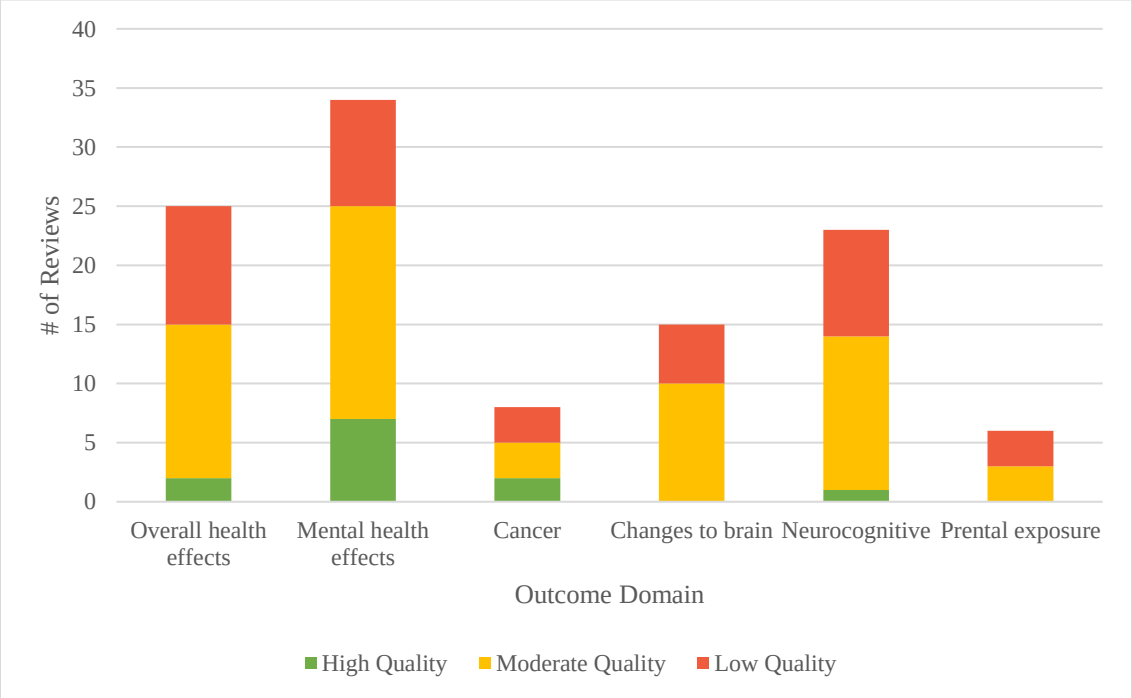
From the 213 full-texts reviewed from the updated search, 48 met our inclusion criteria. Along with the 51 systematic reviews identified from the original overview, a total of 99 systematic reviews were included in the final dataset. The most common reasons for exclusion was incorrect study design (e.g., not a systematic review) (n=96), did not examine health impacts (n=47), or outcomes not related to non-medicinal health effects (n=34). All systematic reviews were published from 2002 to 2020, with over half published since 2016 (n=56). Systematic reviews were conducted in 18 different countries, with the USA conducting most reviews (n=27), followed by the UK (n=19), Australia (n=12), and Canada (n=11). Some reviews reported several outcomes, and as such have been included in more than one domain. Thirty-four reviews reported mental health effects, 25 reported overall health effects, 23 reported neurocognitive effects, 15 reported on changes to the brain, eight reported on cancer, and six reported on prenatal exposure. See *Appendix 3: Study Characteristics* for characteristics of all included reviews.

Figure 1. PRISMA Flow Chart



Thirty-four reviews were of low quality, 53 were moderate quality, and 12 were high quality (Figure 2). Changes to the brain and prenatal exposure had no high-quality reviews. The highest proportion of high quality reviews were reported for the cancer domain (25%; n=2), followed by mental health effects (21%; n=7). Prenatal exposure included the highest proportion of low quality reviews (50%; n=3), followed by overall health effects (40%; n=10), neurocognitive effects (39%; n=9), cancer (38%; n=3), changes to the brain (33%; n=5), and mental health effects (26%; n=9). Quality assessment for all included reviews is provided in *Appendix 4: AMSTAR Quality Assessment.*

Figure 2. Quality Assessment Score of Review, by Outcome Domain[1]



[1] Systematic reviews that reported multiple outcomes may be included in more than one outcome domain

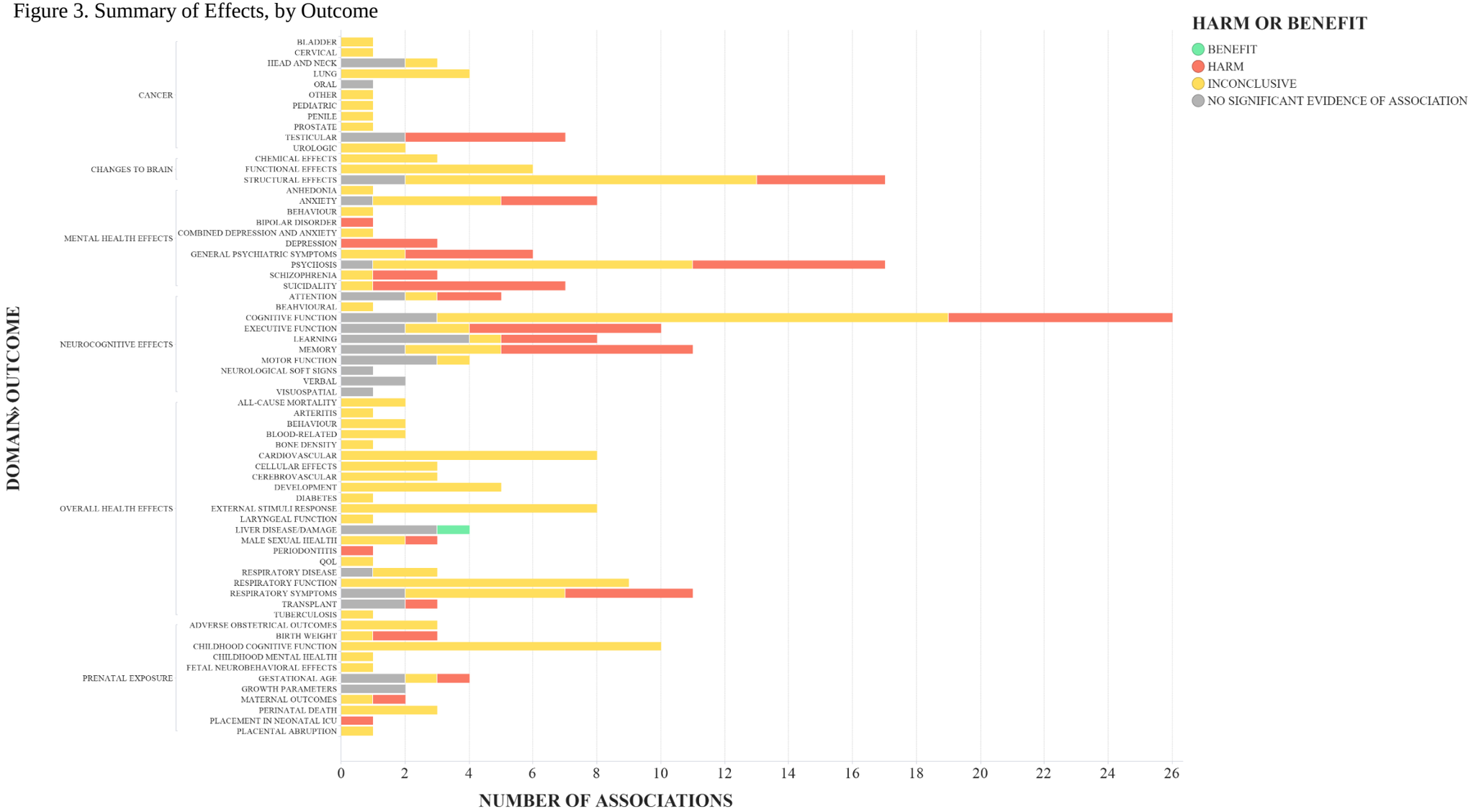
Sixty-six outcomes across the six domains were included in this overview (Figure 3). The most often reported outcomes included: neurocognitive effects, especially cognitive function, memory, and executive function; mental health effects, especially depression and anxiety; and functional and structural changes to the brain.

Thirty-five (53%) of the 66 outcomes did not include a meta-analysis. Therefore, these 35 outcomes were labeled as "consistently inconclusive". Among the remaining 31 outcomes, at least one meta-analysis reported a harmful association for 22 outcomes. Four outcomes consistently reported harm associations in all the pooled analyses (bipolar disorder (n=1), depression (n=3), periodontitis (n=1), and neonatal placement in intensive care unit (n=1)).

At least one non-significant association, or "no evidence of association", were reported for 21 outcomes. Five of these outcomes consistently reported no significant evidence of association (oral cancer, neurological soft signs, verbal fluency, visuospatial function, neonatal growth parameters). Only one non-harmful association, categorized as "benefit", was reported. This outcome was for liver disease, however, overall this outcome's findings were are mixture of non-significant association (n=3) and benefit (n=1).

Detailed results for the six outcome domains are presented below.

Figure 3. Summary of Effects, by Outcome



4.1. Overall Health Effects

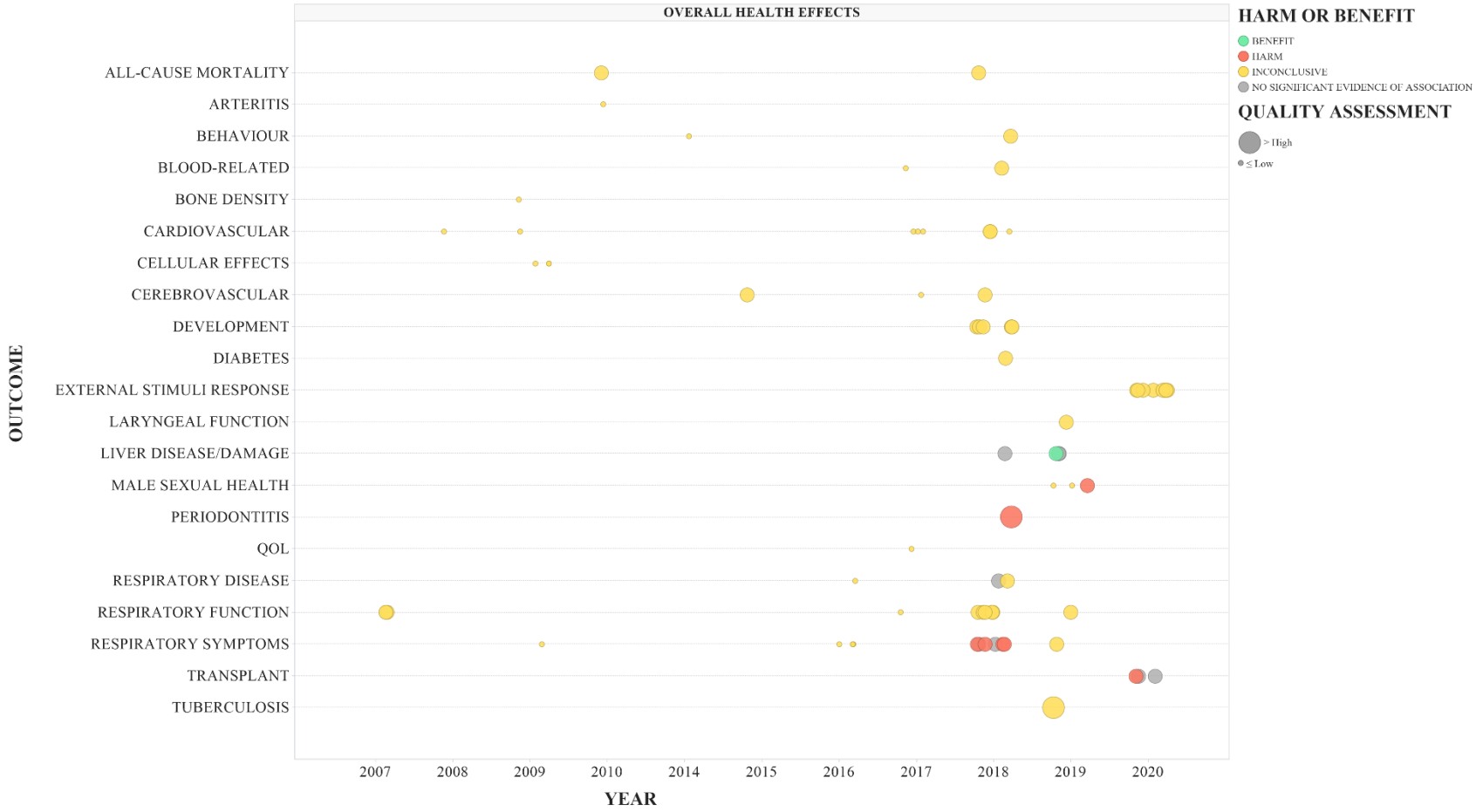
Overall health effects were reported in 25 systematic reviews. Within these reviews, there were 21 different outcome categories. The most reported outcomes were respiratory- and cardiovascular-related outcomes. Only six reviews were published prior to 2015, with over half of the reviews (56%) published between 2018 and 2020 (Figure 4). Most studies were of moderate study quality. Pooled analyses emerged in 2018, with all evidence prior being categorized as inconclusive. One health effect category, periodontitis, reported harms-only findings based on the inclusion of a single meta-analysis.[16]

Given the absence of meta-analyses, all findings were categorized as inconclusive for the following outcomes: all-cause mortality;[17,18] arteritis;[19] behaviour-related outcomes (e.g., sleep);[20,21] blood-related (e.g., coagulation[22] and dyslipidemia[17]); bone density,[23] cardiovascular (e.g., heart attack, ECG abnormalities, cardiovascular mortality);[17,22-25] cellular effects (e.g., genotoxicity, mutagenic, and oncogenic effects);[23] cerebrovascular (e.g., stroke or disease);[17,22,26] body development;[27,28] diabetes;[17] external stimuli response;[29] laryngeal symptoms;[30] quality of life;[31] respiratory function;[30,32-34] and tuberculosis.[35]

Mixed results (e.g., a combination of inconclusive, harmful effect, benefit, or no evidence of association) were reported for liver disease, respiratory disease and symptoms, male sexual function/hormones, and transplant-related outcomes. For liver disease, pooled results from a moderate quality meta-analysis showed no association between cannabis use and progression to hepatic fibrosis (in general population and hepatitis C patients), and advanced liver fibrosis risk, while the prevalence of hepatic steatosis was lower in cannabis users versus non-users.[36] For *respiratory disease*, reviews were inconclusive for cannabis use and COPD, [37] or obstructive lung disease;[32] and non-significant for cannabis use and chronic bronchitis.[32] Cannabis use was associated with *respiratory symptoms* including cough, sputum production, wheezing and dyspnea in one moderate quality meta-analysis including cross-sectional studies.[32] However, in the same review, evidence from prospective cohort studies suggested no evidence for sputum production and cough, indicating that results vary based on study design.[32]

Male sexual health reported inconclusive evidence for effects of cannabis on sexual health/hormones and male factor infertility,[38] however; a moderate quality meta-analysis reported an association between cannabis use and erectile dysfunction.[39] Lastly, a moderate quality meta-analysis of kidney transplant-related outcomes reported that the use of cannabis was significantly associated with increased death-censored graft failure, but was not associated with all-cause allograft failure, or transplant-related mortality.[40]

Figure 4. Level of Evidence, Review Quality, and Year of Publication of Overall Health Effects, by Outcome



4.2. Mental Health

Thirty-four reviews reported 10 outcome categories related to mental health effects. Half of the reviews (50%) were conducted prior to 2015, with the earliest review being conducted in 2004[41] (Figure 5). Review quality was mostly moderate, with meta-analyses conducted consistently over the years. Meta-analyses were absent for three outcomes, therefore all reviews of the following outcomes were categorized as inconclusive: anhedonia (inability to sense pleasure),[42] behaviour-related effects,[41] and combined depression and anxiety.[43] Two outcome included harms-only findings: bipolar disorder, and depression. In a high quality review, Gibbs et al.[44] reported that cannabis use increased the likelihood, severity or duration of manic phases in those with bipolar disorder. Additionally, cannabis use was statistically associated with depression in all three reviews that reported this outcome.[45-47]

The remaining five outcomes resulted in mixed findings (e.g., a combination of inconclusive, harmful effect, and no evidence of association): anxiety, general psychiatric symptoms, psychosis, schizophrenia, and suicidality.

4.2.1. Anxiety

Anxiety was reported in seven systematic reviews. Four reviews did not conduct a meta-analysis, therefore, were categorized as inconclusive.[48-51] One meta-analysis reported a non-significant association between cannabis use and anxiety in young adulthood.[46] Two reviews reported harmful associations between cannabis use and anxiety.[45,52] One meta-analysis reported an association between anxiety and cannabis use disorder.[52]

4.2.2. General Psychiatric Symptoms

Three systematic reviews reported general psychiatric symptom outcomes. One moderate quality meta-analysis explored the effect of acute THC administration versus placebo on psychiatric scores in healthy adults.[53] The authors reported a significant score increase for total symptom severity, positive symptom severity, negative symptom severity, and general psychiatric symptom severity.[53] Meta-analyses were not reported for cannabis use and psychopathological symptoms,[27] and juvenile psychiatric disorders,[41] and were therefore categorized as inconclusive.

4.2.3. Psychosis

Fifteen systematic reviews reported outcomes related to psychosis. All studies exploring cannabis use and age of psychosis onset, or time from cannabis use to psychosis, reported harmful effects of cannabis.[54-57] Results were mixed for symptoms or severity of symptoms. Six reviews did not report a pooled measure of effect, and were categorized as inconclusive. One moderate-quality meta-analysis reported an increased incidence of psychosis-related outcomes in those who had ever used cannabis, and those who were frequent cannabis users.[58] Risk of psychosis or transition to psychosis was reported in five reviews with three categorized as inconclusive;[59-61] one meta-analysis reporting a non-significant association;[62] and one meta-analysis reporting a significant association between cannabis abuse or dependence and transition to psychosis, but not with "any cannabis use".[63]

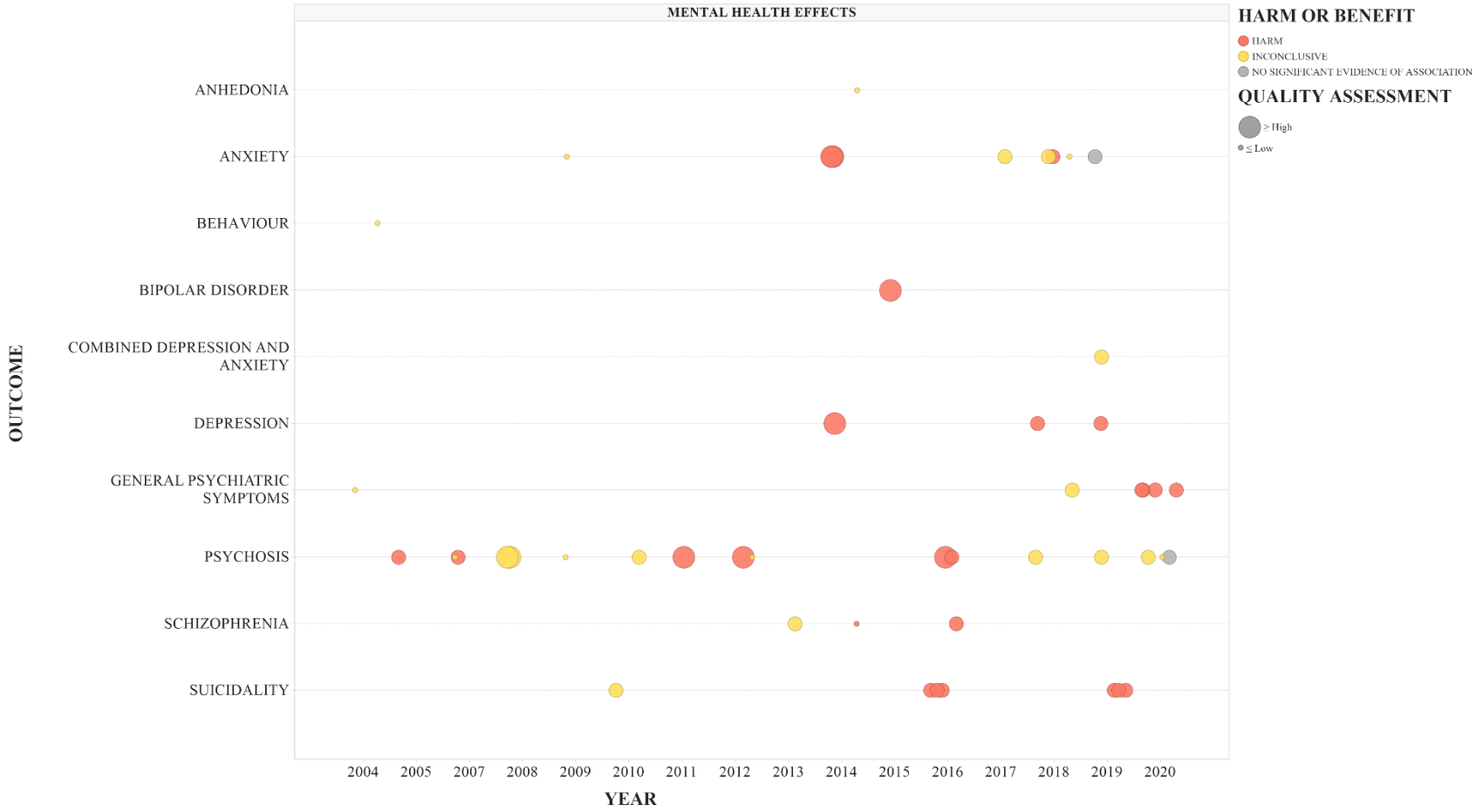
4.2.4. Schizophrenia

Three systematic reviews reported outcomes related to schizophrenia. The associations between cannabis use and onset of schizophrenia[64] was categorized as inconclusive in a moderate quality review. One moderate quality meta-analysis reported a significant association between cannabis use and risk of schizophrenia in participants with psychosis, with a higher risk associated with heavier cannabis use.[65] A low quality review reported that life-time and current cannabis use were both associated with higher schizotypy scores.[66]

4.2.5. Suicidality

Four systematic reviews reported outcomes related to suicidality including suicide death, attempt, and ideation. Results for death by suicide were mixed with one review categorized as inconclusive,[18] and one meta-analysis reporting a significant association between cannabis use and suicide.[67] Suicide attempt was reported in three moderate quality meta-analyses, all reporting evidence of an association between cannabis use and suicide attempt.[46,67,68] Additionally, cannabis use was significantly associated with suicide ideation in both reviews.[46,67]

Figure 5. Level of Evidence, Review Quality, and Year of Publication of Mental Health Effects, by Outcome



4.3. Cancer

Eight systematic reviews examined the effects of cannabis use on 11 types of cancer. One review was published in 2006,[69] with the remaining reviews published between 2015 and 2020 (Figure 6). Evidence of effect was consistent across time. No meta-analytic data existed for bladder,[70] cervical,[70] lung,[37,69-71] other,[71] pediatric,[70] penile,[70] prostate,[70] and urologic cancer.[38,71] A single review examined oral cancer risk, which results in a non-significant association.[71] Mixed results were reported for risk of head and neck, and testicular cancer. Risk of head and neck cancer yielded two reviews concluding no evidence of harm[71,72] and one review categorized as inconclusive.[70] Risk of testicular cancer yielded five harmful associations with long-term, chronic, and current cannabis use, but not with ever used.[70,71,73,74] One review reported a non-significant association between long-term use of cannabis (≥10 years) and seminoma testicular germ cell tumor.[71]

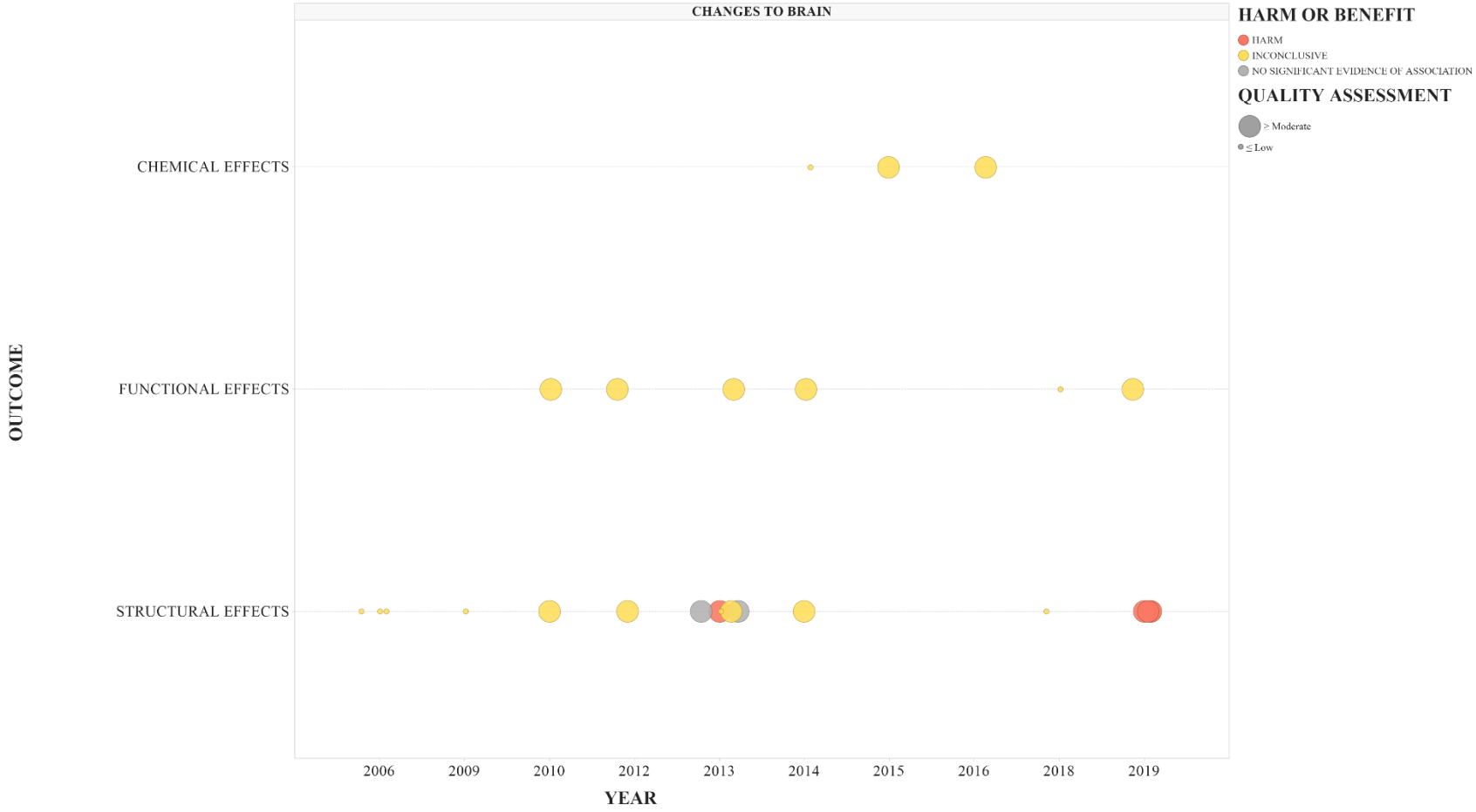
Figure 6. Level of Evidence, Review Quality, and Year of Publication of Effects on Cancer Risk, by Outcome

4.4. Changes to the Brain

Fifteen reviews reported 26 estimations of association between cannabis use and chemical (e.g., changes in level of neurotransmitters), functional (e.g., brain activation and blood flow), and structural (e.g., physical structure of the brain, such as volume) changes to the brain. Publications dates ranged 2006 to 2019, with an even distribution across years (Figure 7). Study quality was consistent across years.

Three reviews reported chemical effects of cannabis including dopamine function,[75] glutamate function,[20] and brain chemistry.[76] None of these reviews reported pooled estimates of effects, and were categorized as inconclusive. Functional effects of cannabis including resting state cerebellar function, functional brain abnormalities, brain activity. None of these reviews reported pooled estimates of effects, and were categorized as inconclusive.[77-82] Most of the estimated associations between cannabis and the brain were related to structural changes. Of the 17 associations reported, 11 were categorized as inconclusive,[23,77,78,80-85] two associations were non-significant between cannabis use and whole brain volume and amygdala volume,[86] and four were harmful. Harmful associations were reported between cannabis use and hippocampal volume,[86,87] and orbitofrontal cortex and lateral orbitofrontal cortex volume.[87]

Figure 7. Level of Evidence, Review Quality, and Year of Publication of Changes to the Brain, by Outcome



4.5. Neurocognitive Effects

Twenty-three systematic reviews published between 2002 and 2020 explored associations between cannabis use and neurocognition. More than half (61%) of the studies have been published since 2018, with only two reviews published prior to 2010 (Figure 8). Reviews were consistent in quality across all years. Neurocognitive outcomes were divided into 10 categories. Neurological soft signs, verbal fluency, and visuospatial outcomes reported non-significant findings only.[88-90] A single review reported on behavioural neurocognitive effects, and was categorized as inconclusive.[82] The remaining six categories yielded mixed results (e.g., a combination of harm, benefit, inconclusive, or no evidence of association): attention, cognitive function, executive function, learning, memory, and motor function.

4.5.1. Attention

Attention was reported in five reviews. One review did not report a pooled analysis and was categorized as inconclusive.[82] Two pooled analyses reported a non-significant association with cannabis.[90,91] Two pooled analyses reported a significant association between cannabis use and reduced attention.[89,92]

4.5.2. Cognitive Function

Seventeen reviews reported 26 cognitive function associations. The majority of the associations were categorized as inconclusive (n=16). A notable moderate quality systematic review synthesized the effect of cannabis use on cognitive outcomes in older adults, stratified by clinical diagnosis of: dementia, Parkinson's disease, multiple sclerosis, HIV, chronic pain, and healthy older adults.[93] Pooled estimates of effects were not reported for any of these comparisons, and were categorized as inconclusive. In two moderate quality meta-analyses, [91,94] and one low quality meta-analysis of young psychosis patients,[90] there was no association between cannabis use and cognitive function. Cognitive flexibility yielded mixed results with one meta-analysis reporting non-significant findings in young patients with psychosis,[90] and a harmful association in another meta-analysis of adult chronic cannabis users.[92] Other harmful effects were reported for: cognitive impulsivity (moderate quality),[92] global cognition (moderate quality),[91,95] and delay discounting (low quality);[96] and between heavy or frequent cannabis use and overall neurocognitive effect (low quality).[89]

4.5.3. Executive Function

Five reviews reported 10 estimates of association between cannabis use and executive function. Cannabis use was associated with poorer overall executive function,[91] decision-making,[91] and working memory[90] in adults; and abstraction/shifting, inhibition, and working memory in adolescents and young adults.[89] There was a non-significant association between cannabis use and working memory,[91] and conceptual set-shifting;[90] and inconclusive findings for inhibition in adults.[64]

4.5.4. Learning

Learning was reported in five systematic reviews, of which four were low quality.[64,89,90,97] Processing speed was mixed with one meta-analysis reporting a non-significant association,[90] and one reported a harmful association in adolescents and young adults.[89] Results for IQ were also mixed, with one review reporting a harmful effect,[90] and reporting inconclusive evidence.[64] Overall learning was mixed with one meta-analysis reported a harmful association in adolescents and young adults,[89] and one review reporting a non-significant association.[97] For information processing, there was one moderate quality meta-analysis that reported a non-significant association.[91]

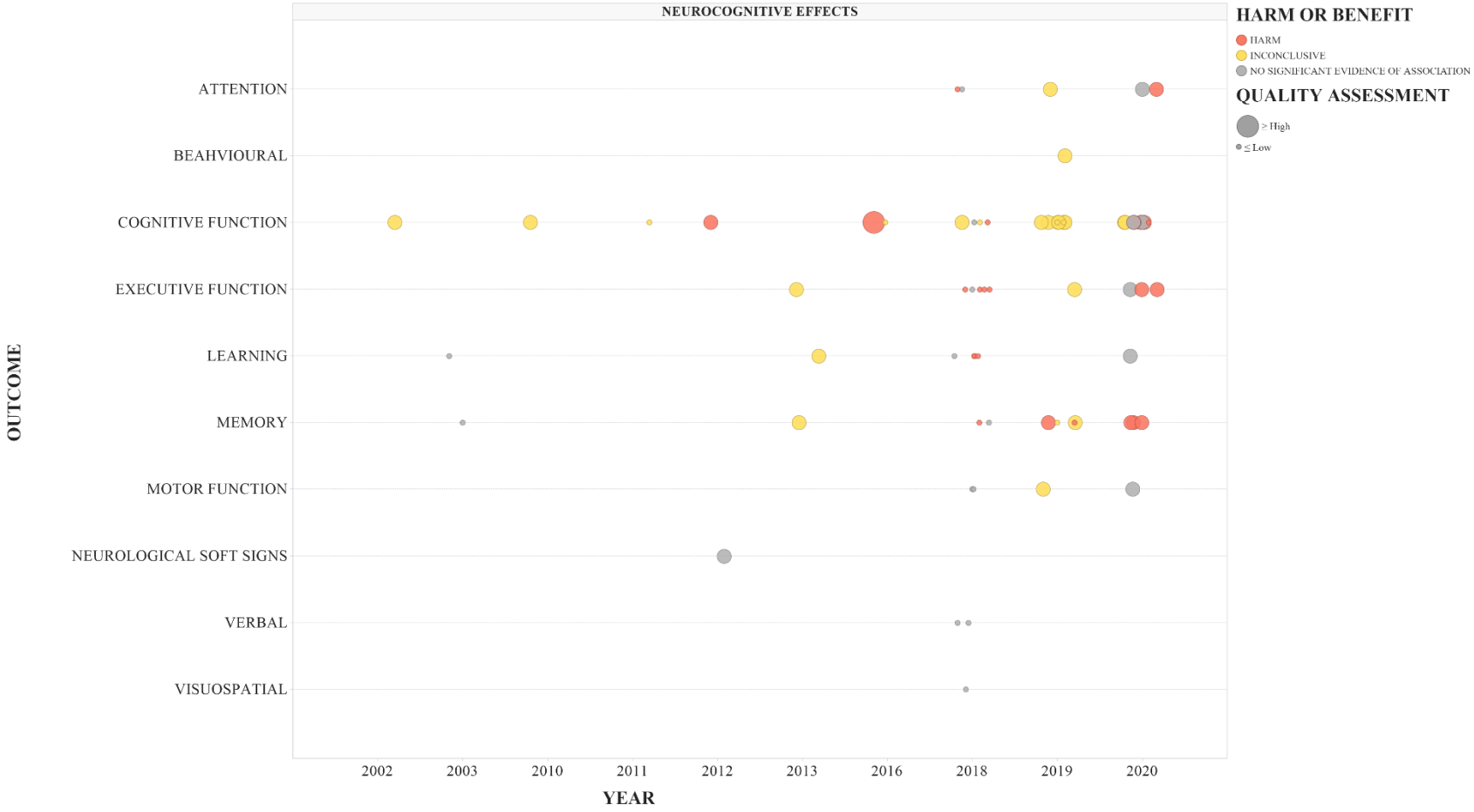
4.5.5. Memory

Memory was explored in nine reviews, reporting 11 estimates. Six of the 11 estimates between cannabis use and memory were harmful,[89,91,92,98,99] with three associations yielding inconclusive results,[82,90,98] and two reporting a non-significant association.[90,97]

4.5.6. Motor Function

Four reviews reported outcomes related to motor function.[82,89,90,92] One review was categorized as inconclusive;[82] and three reviews reported no evidence of an association between cannabis use and motor function, including one review of adolescent and young adults with psychosis,[89] and one review of chronic/heavy users of cannabis.[92]

Figure 8. Level of Evidence, Review Quality, and Year of Publication of Neurocognitive Effects, by Outcome



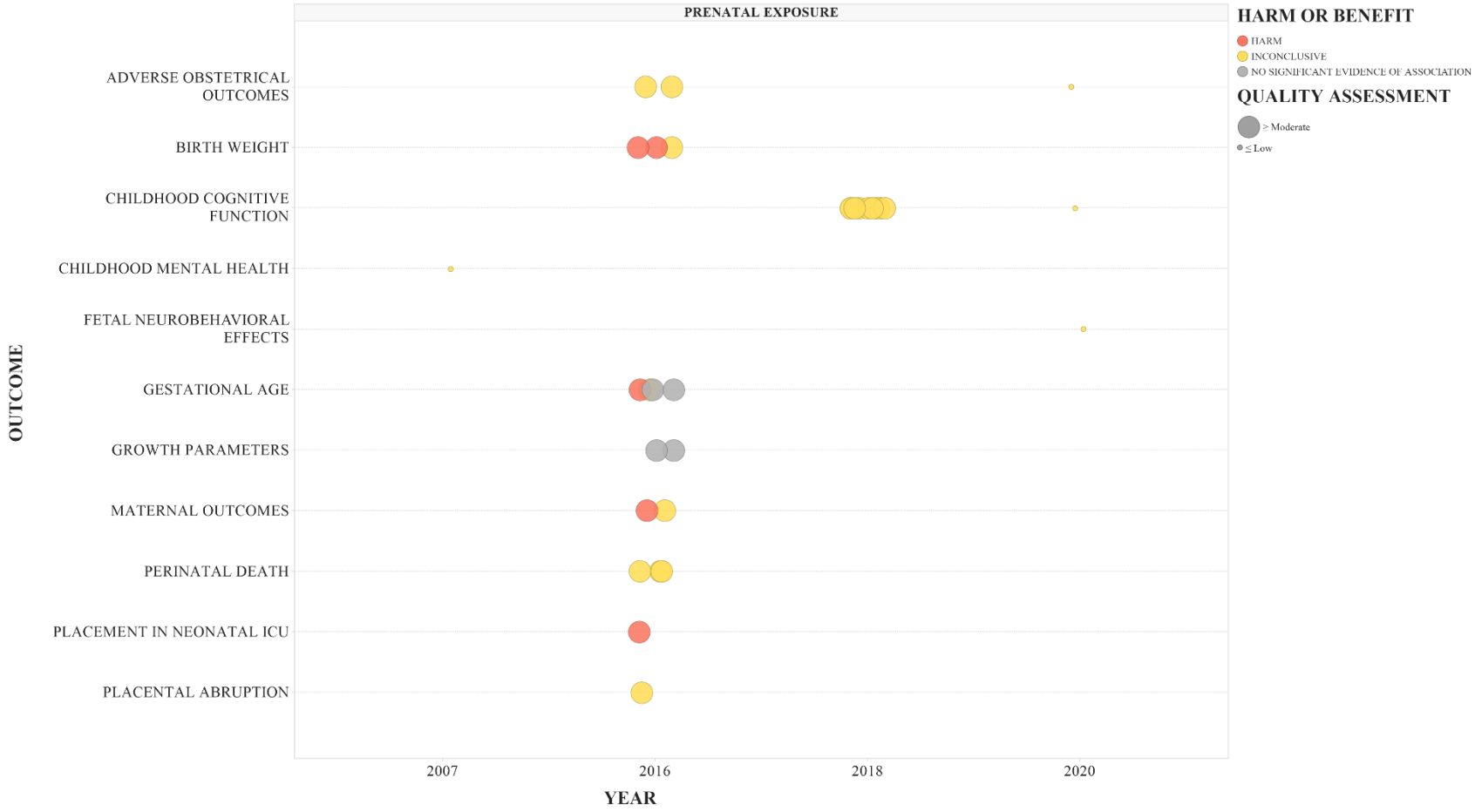
4.6. Prenatal Exposure

Six systematic reviews explored prenatal cannabis exposure and birth, maternal, and childhood-related outcomes (Figure 9). Prenatal cannabis exposure includes in-utero exposure to cannabis (i.e., cannabis use during pregnancy). No reviews specifically exploring perinatal cannabis exposure (i.e., cannabis exposure after birth via breastmilk) met the inclusion criteria for this overview. Moderate quality meta-analyses were published in 2016 and 2018, with low-quality systematic reviews published in 2007 and 2020. Adverse obstetrical outcomes,[100,101] childhood cognitive function,[102] childhood mental health,[103] fetal neurobehavioural effects,[100] growth parameters (e.g., neonatal head circumference, and length),[104] perinatal death,[101] and placental abruption[101] were categorized as inconclusive, or reported no significant evidence of association..

Mixed results were reported for birth weight, gestational age at birth, and maternal outcomes. Prenatal cannabis exposure was associated with low birth weight in two reviews,[101,104] while small for gestational age was categorized as inconclusive.[101] Gestational age at birth was not associated with prenatal cannabis exposure in one review,[104] and inconclusive in another.[101] Preterm delivery was associated with prenatal cannabis exposure in one meta-analysis[101] but reported a non-significant association in another meta-analysis.[104] For maternal outcomes, a harmful effect was reported for maternal anemia, but not for other maternal outcomes (e.g., labour and delivery, maternal diabetes, or postnatal problems).[104]

Placement in neonatal intensive care unit was associated with prenatal cannabis exposure in one review.[104] This was the only outcome for prenatal exposure with only a harmful association concluded in the single systematic review completed to date.

Figure 9. Level of Evidence, Review Quality, and Year of Publication of Prenatal Exposure, by Outcome



4.7. Other Specific Populations

Few systematic reviews included specific populations other than pregnant women and their children. A detailed description of findings for specific populations can be found in *Appendix 2: Supplementary Tables and Figures*. Adolescent and young adults were the population of interest in eight systematic reviews. Five of these reviews reported on mental health effects including anxiety, depression, psychosis, general psychiatric symptoms, and suiciality.[41,43,45,46,48] Mental health effects for adolescents and young adults were mostly categorized as inconclusive, though harmful associations of cannabis use were reported for anxiety and depression in people aged 10-24, and for suicide ideation and attempt for young adults (Table 3).[46] Two reviews reported on neurocognitive effects.[64,89] In adolescents and young adults, a harmful association was reported between cannabis use and memory, attention, overall neurocognitive effects, executive function, speed of processing, and learning.[89] Findings on inhibition and IQ were categorized as inconclsuive.[64] One review explored pubertal development, but included zero studies on any of the pubertal outcomes including pubertal timing and tempo, and final weight and height.[28]

Few reviews offered stratified analyses by age or sex. Adults over 50 years was the population of interest in one review of neurocognitive effects of cannabis, yielding inconclusive results.[93] Nine reviews reported stratified findings by age for changes to the brain,[76,78,81] mental health effects,[45,59] neurocognitive effects,[89,95] and prenatal exposure.[102,105] All results reported from age-stratified analysis for changes to the brain and prenatal exposure, were categorized as inconclusive. For mental health effects, one subgroup analysis of adolescents (10-18 years) and young adults (19-24 years), reported that the association between cannabis use and mental health disorders remained significant for adolescents, but not for young adults.[45] For changes to the brain, there was no significant difference in the harmful effect size by age category for overall neurocognitive effects.[89] In another meta-analysis, age was not a significant moderator of the association between cannabis use and neurocognitive performance.[95]

One systematic review provided sex-dependent interactions between cannabis use and adolescent brain development, and was categorized as inconclusive.[64] There were no other demographic stratifications presented in the literature such as ethnicity, Indigenous populations, or 2SLGBTQ+ populations.

Table 3. Health Effects of Cannabis by Specific Populations

	Age Specific			Sex Specific		
	No Significant Evidence of Association	**Inconclusive**	**Harm**	**No Significant Evidence of Association**	**Inconclusive**	**Harm**
Overall Health Effects		• Development in adolescents[28]				
Mental Health Effects	• Mental health disorders for young adults[45]	• Juvenile psychiatric disorder[41] • Behavioural problems[41] in adolescents and young adults • Psychosis in adolescents and young adults[43] • Schizophrenia onset in adolescents and young adults [64] • Combined depression and anxiety in adolescents and young adults[43] • Risk of psychosis stratified by age[59] • Anxiety in adolescents and young adults[48]	• Anxiety in adolescents and young adults[45] • Depression in adolescents and young adults[45,46] • Suicidal ideation in young adults[46] • Suicide attempts in young adults[46] • Mental health disorders for adolescents[45]			
Cancer						
Changes to the Brain		• Inhibition in adolescents and young adults[64] • IQ in adolescents and young adults[64] • White matter stratified by age[81] • Brain chemistry stratified by age[76] • Functional changes stratified by age[78] • Structural changes stratified by age[78] • Brain activity stratified by age[81]			• Brain volume in adolescents[64]	

Neurocognitive Effects	• Speed of processing in adolescents and young adults[89] • Motor functioning in adolescents and young adults[89] • Verbal/language in adolescents and young adults[89] • Visuospatial in adolescents and young adults[89]	• Cognitive outcomes in older adults[93] • Memory in adolescents and young adults[64]	• Memory in adolescents and young adults[89] • Attention in adolescents and young adults[89] • Overall neurocognitive effects in adolescents and young adults[89] • Executive functioning in adolescents and young adults[89] • Learning in adolescents and young adults[89] • Neurocognitive performance for all age categories[95]			
Prenatal Exposure		• Childhood perceptive ability stratified by age[102] • Childhood general cognitive function stratified by age[102] • Childhood memory stratified by age [102] • Childhood impulse control stratified by age [102] • Childhood IQ stratified by age [102] • Childhood reading comprehension[102] • Childhood attention stratified by age [102] • Childhood cognitive impairment stratified by age [105]				

5. Discussion

There are a considerable number of systematic reviews on physical and mental health effects related to non-medical cannabis use, with the majority being of moderate quality. Reviews were published between 2002 and 2020, with over 60% being published since 2015. This emerging research interest in cannabis and health-related effects coincides with the growing momentum to legalize non-medical cannabis, beginning in Washington and Colorado in 2012 and followed by 13 more states,[106] Canada (2018),[107] Uruguay (2013),[107] the country of Georgia (2018),[108] South Africa (2018),[109] and the Australian Capital Territory (2020).[110]

The recent surge of literature was most evident for neurocognitive effects, overall health effects, and prenatal exposure domains, with nearly all pooled estimates being reported after 2016. Of note is the early and consistent interest in meta-analyses of effects of cannabis on mental health since 2005, likely due to the long-standing interest in the psychoactive effects of THC.[107] The pooled estimates of effect are important for policy making, as they indicate the strength of association. A growing number of meta-analyses will allow for more informed recommendations.

Harmful effects were exclusively reported for bipolar disorder and depression. Mixed findings were reported for anxiety, general psychiatric symptoms, psychosis, schizophrenia, and suicidality. However, we have not explored the strength and quality of the underlying primary studies themselves so the findings of these reviews must be understood within that context. Nonetheless, at this overview level, there are harms associated with cannabis use in some mental illnesses. These findings continue to support the recommendations that people experiencing mental illnesses should abstain from cannabis use.

Mixed results were reported for respiratory-related outcomes. For respiratory disease, no meta-analyses have been reported for chronic obstructive lung disease, resulting in the inconclusive findings reported in this overview. In one meta-analysis of cross-sectional studies, cannabis use was not significantly associated with chronic bronchitis. No meta-analyses were reported for cannabis use and respiratory function including airway response or resistance, forced vital capacity, FEV_1, or exercise induced asthma. This does not mean that no harm exists in the

primary studies examining these respiratory diseases or functions, but that meta-analyses on these outcomes is warranted.

Meta-analyses of *cross-sectional studies* reported harmful associations for respiratory symptoms including wheezing, coughing, dyspnea, and sputum production, though meta-analyses of *prospective cohort studies* suggested no association. Taking all of this evidence together, we do not have convincing evidence of a harmful association between cannabis use and respiratory outcomes, though it is evident that some harm exists. However, at this time it is not clear whether these harmful associations are a result of the cannabis substance, the inhalation of it, or a combination of both. This highlights the need for a more robust review of the literature to determine if the association between cannabis use and respiratory outcomes is due to the effects of cannabis, or the effects of inhalation of cannabis smoke. Overall, these findings support recommendations that people with existing respiratory conditions should abstain from inhaling cannabis.

The findings on the impact of cannabis use on neurocognition are mixed. For the outcomes of attention, cognitive function, executive function, learning, and memory, multiple meta-analyses reported a total of 24 harmful associations, and 13 non-significant associations. An additional 23 systematic reviews did not conduct meta-analysis, and were categorized as inconclusive. As a result, no conclusions can be drawn on whether or not cannabis use is harmful for neurocognition for the general population. However, when exploring the systematic reviews on adolescents and young adults only, the evidence appears to be more consistent. In adolescents and young adults, there is evidence of harm for cannabis use and attention, memory, learning, executive function, and overall neurocognition. Taken together, it seems prudent to continue to support recommendations that people under the age of 18 should not consume cannabis.

Results were categorized as inconclusive for pre/postnatal effects including adverse obstetrical outcomes, childhood cognitive function, childhood mental health, fetal neurobehavioural effects, perinatal death, and placental abruption. Within these outcomes, meta-analyses have not been reported and so for the purposes of this overview, no conclusions can be drawn. In addition, mixed results were reported for birthweight, gestational age at birth, and maternal outcomes. Harmful associations are reported for these outcomes; however, there is also evidence of no

association (e.g., non-significant findings), or inconclusive findings from reviews without pooled estimates. Finally, for the outcome of neonatal placement in intensive care unit, the single systematic review identified reported harm associated with cannabis use. Taken together, the body of literature identified many gaps in our knowledge of the association between cannabis use during pregnancy and health outcomes. Given our gaps in knowledge and severity of possible consequences if harmful during pregnancy, recommendations that cannabis should not be used during pregnancy should continue.

No significant evidence of an association (e.g., non-significant association) was reported consistently for five outcomes including oral cancer, neurological soft signs, verbal fluency, visuospatial function, and neonatal growth parameters. However, in many cases, evidence on each of these health outcomes is limited to one meta-analysis; more evidence is required to draw strong conclusions.

Even with rapidly accumulating evidence, there are few conclusions that can be drawn about the impact of cannabis on health outcomes. However, this does not mean that cannabis is a benign substance, or that no harm exists. For the outcomes where harm was reported, we are unable to estimate the level or consistency of these harmful associations. With this in mind, guidelines such as Canada's Lower-Risk Cannabis Use Guidelines[111] should continue to be recommended to guide people's cannabis use, including when not to consume. Given our evolving understanding of the effects of cannabis, it seems prudent to continue to develop policy and regulations through a harm reduction lens.

5.1. Supporting Evidence

The evidence reported in this overview are consistent with the findings reported in the 2017 *National Academies of Science, Engineering, and Medicine* (NASEM) report[112] on cannabis and cannabinoids. For overall health effects, we support the NASEM report's conclusion of limited or no evidence for many overall health effects, however, the NASEM report concluded that substantial evidence exists for cannabis smoking and worsening respiratory symptoms; a finding not evident from this overview. For mental health effects, evidence of harm exists between cannabis use and suicide, depression, symptoms of mania, and the development of schizophrenia

or other psychoses. Limited evidence of statistical associations between cannabis use and anxiety, symptoms of schizophrenia and general psychiatric symptoms exist. These findings are supported by NASEM.[112]

For cancer, there is no, or insufficient evidence to support an association between cannabis and any cancer other than testicular cancer.[112] For neurocognitive effects, evidence from NASEM report[112] conclude that moderate evidence of exists for *acute* effects of cannabis on learning, memory, and attention, but limited evidence of for sustained abstinence from cannabis on these outcomes. This is echoed in our overall mixed findings for effects of cannabis on learning, memory, and attention. There were no conclusions made about chemical, structural, or functional changes to the brain in the NASEM report.[112]

Finally, for prenatal exposure, evidence between the NASEM report[112] and this overview are consistent. There is evidence of associations between prenatal cannabis exposure and low birth weight, maternal outcomes, and neonatal admission to the ICU, with insufficient evidence reported for other outcomes (e.g., outcomes in childhood).

5.2. Gaps in the Literature

It is clear by the evidence presented in this report and elsewhere that an abundance of cannabis-related research exists; however, future research is still required to fill gaps in our knowledge. There is very limited evidence on populations other than "general adults." We identified very few reviews that exclusively included a specific population such as pregnant women, children, adolescents, or older adults; or that stratified their findings by age or sex. Furthermore, there were no reviews that specifically included Indigenous Peoples, ethnic minorities, or 2SLGBTQ+ populations. Given the difference in health needs, status, and outcomes of these specific populations, further research on these populations is required.

Mode of consumption is another important factor when exploring the health effects of cannabis. For example, respiratory-related outcomes may vary between inhaled cannabis compared to edible cannabis, which would influence the recommendations for cannabis use when considering at-risk populations (e.g., those with pre-existing respiratory symptoms). Additionally, as the

metabolism of individuals differs, the effects of inhaled or ingested cannabis may differ depending on a person's weight, age, and sex.

Lastly, stronger study designs are needed to understand the direction of association between cannabis use and health effects. Much of the evidence reported from the included reviews relies on case-control and cross-sectional data. For this reason, it is difficult to determine the direction of association, or causality, between cannabis use and the health outcome of interest. For example, a significant association between cannabis use and suicide attempt from a meta-analysis of cross-sectional data only tells us that an association exists, but it is not possible to tease apart whether cannabis use started as a means to self-medicate suicidality, or if cannabis use may have contributed to a suicidal attempt. Pooled analyses of longitudinal studies, or randomized control trials, will provide a better understanding of the direction of association between cannabis use and health effects.

5.3. Limitations

There are some limitations to this overview. Medicinal use of cannabis, such as adverse effects from prescribed cannabis, was not considered for this overview, therefore any possible therapeutic or medical effects of cannabis were not captured. In addition, given the inconsistencies in defining cannabis concentration or exposure (e.g., frequency of use, mode of administration), we are unable to provide dose-response conclusions. As previously mentioned, the inclusion of reviews based on cross-sectional and cohort data did not allow us to infer causation, or indicate the direction of association between cannabis use and health effects. Additionally, given that this is an update of a previously completed overview, there are some differences in the interpretation of results from the included reviews. Lastly, much of the evidence was categorized as inconclusive given the lack of available data from pooled analyses. Without pooled estimates, we are unable to determine the effect size, if any, that cannabis use may have on health outcomes.

6. Conclusion

Despite extensive interest in cannabis-related research, there are few or mixed findings from published meta-analyses. Based on the evidence herein, it is reasonable to conclude that those experiencing mental illnesses, those with existing respiratory conditions, people under the age of 18 years, and women who are pregnant should abstain from using cannabis. More evidence, particularly high-quality meta-analyses on longitudinal studies or randomized controlled trials, is required to understand the causal effect of cannabis on other aspects of health. As interest in the health effects of cannabis continue to rise and more studies emerge, more conclusive evidence may become available in the coming years.

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Appendix 1: Search Strategy

Medline

1. Cannabis/ae, de, pd, po, to [Adverse Effects, Drug Effects, Pharmacology, Poisoning, Toxicity]

2. exp Marijuana Abuse/

3. ((bhang or bhangs or bhangstar or cannabutter or cannabis* or doobie* or ganga or gangas or ganja or ganjas or grass or hash* or hashish* or hemp or hemps or honeycomb or mary jane* or marihuana* or marijuana* or moon rock or pot or reefer* or roach* or shatter or weed) adj10 (abus* or addiction* or addictive* or adverse event* or adverse reaction* or behavioral or behavioural or blood pressure or cancer* or (behavior adj1 chang*) or (behaviour adj1 chang*) or cogniti* or death* or dependenc* or depressi* or (drug* adj3 interact*) or effect or effects or harm or harms or impact or impacts or impair* or intoxicat* or lung or lungs or mania or morbidit* or mortalit* or overdos* or poison* or psycho* or pulmonary or respiratory or risks or safety or suicid* or toxic*)).tw.

4. 1 or 2 or 3

5. limit 4 to (english or french)

6. limit 5 to (case reports or comment or editorial or letter)

7. 5 not 6

8. limit 7 to systematic reviews

9. ((systematic or critical or scoping) adj3 (overview* or review* or synthesis)).tw.

10. 7 and 9

11. limit 7 to meta analysis

12. 8 or 10 or 11

Embase

1. cannabis/ae, it, to [Adverse Drug Reaction, Drug Interaction, Drug Toxicity]

2. cannabis addiction/

3. ((bhang or bhangs or bhangstar or cannabutter or cannabis* or doobie* or ganga or gangas or ganja or ganjas or grass or hash* or hashish* or hemp or hemps or honeycomb or mary jane* or marihuana* or marijuana* or moon rock or pot or reefer* or roach* or shatter or weed) adj10 (abus* or addiction* or addictive* or adverse event* or adverse reaction* or behavioral or behavioural or blood pressure or cancer* or (behavior adj1 chang*) or (behaviour adj1 chang*) or cogniti* or death* or dependenc* or depressi* or (drug* adj3 interact*) or effect or effects or harm or harms or impact or impacts or impair* or intoxicat* or lung or lungs or mania or morbidit* or mortalit* or overdos* or poison* or psycho* or pulmonary or respiratory or risks or safety or suicid* or toxic*)).tw.

4. 1 or 2 or 3

5. limit 4 to (english or french)

6. limit 5 to (conference abstract or editorial or letter)

7. 5 not 6

8. limit 7 to (meta analysis or "systematic review")

9. ((systematic or critical or scoping) adj3 (overview* or review* or synthesis)).tw.

10. 7 and 9

11. 8 or 10

Cochrane Database of Systematic Reviews

((bhang or bhangs or bhangstar or cannabutter or cannabis* or doobie* or ganga or gangas or ganja or ganjas or grass or hash* or hashish* or hemp or hemps or honeycomb or mary jane* or marihuana* or marijuana* or moon rock or pot or reefer* or roach* or shatter or weed) adj10 (abus* or addiction* or addictive* or adverse event* or adverse reaction* or behavioral or behavioural or blood pressure or cancer* or (behavior adj1 chang*) or (behaviour adj1 chang*) or cogniti* or death* or dependenc* or depressi* or (drug* adj3 interact*) or effect or effects or harm or harms or impact or impacts or impair* or intoxicat* or lung or lungs or mania or morbidit* or mortalit* or overdos* or poison* or psycho* or pulmonary or respiratory or risks or safety or suicid* or toxic*)).tw.

HTA Database

1. ((bhang or bhangs or bhangstar or cannabutter or cannabis* or doobie* or ganga or gangas or ganja or ganjas or grass or hash* or hashish* or hemp or hemps or honeycomb or mary jane* or marihuana* or marijuana* or moon rock or pot or reefer* or roach* or shatter or weed) adj10 (abus* or addiction* or addictive* or adverse event* or adverse reaction* or behavioral or behavioural or blood pressure or cancer* or (behavior adj1 chang*) or (behaviour adj1 chang*) or cogniti* or death* or dependenc* or depressi* or (drug* adj3 interact*) or effect or effects or harm or harms or impact or impacts or impair* or intoxicat* or lung or lungs or mania or morbidit* or mortalit* or overdos* or poison* or psycho* or pulmonary or respiratory or risks or safety or suicid* or toxic*)).tw.
2. Limit 1 to (English or French)

PsycINFO

1. ((bhang or bhangs or bhangstar or cannabutter or cannabis* or doobie* or ganga or gangas or ganja or ganjas or grass or hash* or hashish* or hemp or hemps or honeycomb or mary jane* or marihuana* or marijuana* or moon rock or pot or reefer* or roach* or shatter or weed) adj10 (abus* or addiction* or addictive* or adverse event* or adverse reaction* or behavioral or behavioural or blood pressure or cancer* or (behavior adj1 chang*) or

(behaviour adj1 chang*) or cogniti* or death* or dependenc* or depressi* or (drug* adj3 interact*) or effect or effects or harm or harms or impact or impacts or impair* or intoxicat* or lung or lungs or mania or morbidit* or mortalit* or overdos* or poison* or psycho* or pulmonary or respiratory or risks or safety or suicid* or toxic*)).tw.

2. exp cannabis/
3. marijuana usage/
4. 2 or 3
5. exp Major Depression/ or exp "Side Effects (Drug)"/ or exp Risk Factors/
6. exp mental disorders/
7. 5 or 6
8. 4 and 7
9. 1 or 8
10. limit 9 to (english or french)
11. limit 10 to (abstract collection or "column/opinion" or "comment/reply" or editorial or letter)
12. 10 not 11
13. ((systematic or critical or scoping) adj3 (overview* or review* or synthesis)).tw.
14. 12 and 13
15. (meta analysis or metanalysis or metaanalysis).tw.
16. 12 and 15
17. meta analysis/
18. 12 and 17
19. 14 or 16 or 18

CINAHL

1. (MH "Cannabis/AE/CT/DE/PO")
2. ((bhang or bhangs or bhangstar or cannabutter or cannabis* or doobie* or ganga or gangas or ganja or ganjas or grass or hash* or hashish* or hemp or hemps or honeycomb or mary jane* or marihuana* or marijuana* or moon rock or pot or reefer* or roach* or shatter or weed) N10 (abus* or addiction* or addictive* or adverse event* or adverse reaction* or behavioral or behavioural or blood pressure or cancer* or (behavior N1 chang*) or (behaviour N1 chang*) or cogniti* or death* or dependenc* or depressi* or (drug* N3 interact*) or effect or

effects or harm or harms or impact or impacts or impair* or intoxicat* or lung or lungs or mania or morbidit* or mortalit* or overdos* or poison* or psycho* or pulmonary or respiratory or risks or safety or suicid* or toxic*)) [Title/Abstract]

3. 1 or 2
4. Limit 3 to (English or French)
5. ((systematic or critical or scoping) N3 (overview* or review* or synthesis))[Title/Abstract]
6. (meta analysis or metanalysis or metaanalysis)[Title/Abstract]
7. 5 or 6
8. 4 and 7

Appendix 2: Supplementary Tables and Figures

Table 4. Explanation of Changes from Original Report to Updated Report

Author (Year)	Outcome	Original categorization of findings	Updated Findings	Reason for change
Quickfall[113] (2006)	changes in dopamine	harm	excluded	revised inclusion criteria excluded reviews with only one database searched
Lindsey[114] (2012)	cross-interaction with drugs	harm	excluded	revised inclusion criteria excluded multi-drug interaction
Schwitzer[115] (2015)	visual processing	harm	excluded	revised inclusion criteria excluded reviews with only one database searched
Schoeler[116] (2016)	memory	harm	excluded	revised inclusion criteria excluded reviews with only one database searched
Schoeler[117] (2016)	relapse	harm	excluded	revised inclusion criteria excluded relapse
Smith[118] (2014)	behavioural inhibition	inconclusive	excluded	revised inclusion criteria excluded cannabis mixed with other substances
Wrege[119] (2014)	neuroimaging	harm	excluded	revised inclusion criteria excluded reviews with only one database searched
English[120] (1997)	birth weight	harm	excluded	revised inclusion criteria excluded reviews with only one database searched
Viteri[121] (2015)	congenital anomalies, long-term implications of prenatal cannabis exposure	harm	excluded	revised inclusion criteria excluded reviews with only one database searched

Author (Year)	Outcome	Original categorization of findings	Updated Findings	Reason for change
Macleod[122] (2004)	social problems	inconclusive	excluded	revised inclusion criteria excluded cannabis mixed with other substances
Asbridge[123] (2012)	motor-vehicle collisions	harm	excluded	revised inclusion criteria excluded social effects
Le Bec[124] (2009)	psychosis, psychotic symptoms	harm	excluded	revised inclusion criteria excluded reviews with only one database searched
Lorenzetti[125] (2010)	brain changes, psychopathological symptoms	harm	excluded	revised inclusion criteria excluded reviews with only one database searched
Hackam[26] (2015)	stroke	harm	inconclusive	Not a meta-analysis, therefore results re-categorized as inconclusive
Grotenhermen[19] (2010)	arteritis	no evidence of harm	inconclusive	Not a meta-analysis, therefore results re-categorized as inconclusive
Huang[70] (2015)	lung cancer	no evidence of harm	inconclusive	Not a meta-analysis, therefore results re-categorized as inconclusive
Garfield[42] (2014)	anhedonia	harm	inconclusive	Not a meta-analysis, therefore results re-categorized as inconclusive
Ruiz-Veguilla[88] (2012)	neurological soft signs	harm	no evidence of association	In meta-analytic evidence of two studies, no evidence of association
Colizzi [126] (2016)	glutamate function	harm	inconclusive	Not a meta-analysis, therefore results re-categorized as inconclusive
Tetrault[33] (2007)	pulmonary function	harm	inconclusive	Not a meta-analysis, therefore results re-categorized as inconclusive

Author (Year)	Outcome	Original categorization of findings	Updated Findings	Reason for change
Martin-Santos[77] (2010)	global functioning	harm	inconclusive	Not a meta-analysis, therefore results re-categorized as inconclusive

Table 5. Detailed Results of Cannabis Use and Health Effects for Specific Populations

	Adolescents and Young Adults	Older Adults	Stratified by Age	Stratified by Sex
Overall Health Effects	*Development* Inconclusive –systematic review[28]			
Mental Health Effects	*Juvenile Psychiatric Disorder* Inconclusive - systematic review[41] *Behavioral Problems* Inconclusive - systematic review[41] *Psychosis* Inconclusive - systematic review[43] *Schizophrenia Onset* Inconclusive – systematic review[64] *Combined Depression and Anxiety* Inconclusive - systematic review[43] *Depression*		*Mental Health Disorders* Harm (adolescents)/No association (young adults) - Subgroup analysis of adolescents (10-18 years) and young adults (19-24 years) report that the association between cannabis use and mental health disorders remains significant for adolescents, but not for young adults.[45] *Risk of Pscyhosis* Inconclusive – systematic review[59]	

	Adolescents and Young Adults	Older Adults	Stratified by Age	Stratified by Sex
	Harm - The odds of developing depression for cannabis users in young adulthood compared with nonusers was significant [46] Harm - Pooled analysis suggests a significantly harmful association between cannabis use and depression for people aged 10-24 years[45] *Anxiety* No association - There was a non-significant association between cannabis use and anxiety in young adulthood[46] Harm - Pooled analysis suggests a significantly harmful association between cannabis use and anxiety for people aged 10-24 years[45] Inconclusive – systematic review[48] *Suicidal Ideation* Harm - There was a significant association between cannabis use and suicidal ideation in young adulthood[46] *Suicide Attempts*			

	Adolescents and Young Adults	Older Adults	Stratified by Age	Stratified by Sex
	Harm - There was a significant association between cannabis use and suicidal attempt in young adulthood[46]			
Changes to the Brain			*Brain Chemistry* Inconclusive – systematic review[76] *Functional Changes* Inconclusive – systematic review [78] *Structural Changes* Inconclusive – systematic review [78] *Brain Activity* Inconclusive – systematic review[81] *White Matter* Inconclusive – systematic review[81]	*Brain Volume in Adolescents* Inconclusive – systematic review[64]

	Adolescents and Young Adults	Older Adults	Stratified by Age	Stratified by Sex
Neurocognitive Effects	*Inhibition* Inconclusive - systematic review[64] *IQ* Inconclusive - systematic review[64] *Memory* Inconclusive - systematic review[64] Harm - In adolescents and young adults, significant impairment of delayed memory due to cannabis was found[89] *Attention* Harm - In adolescents and young adults, significant impairment due to cannabis was found[89] *Overall Neurocognitive Effect* Harm - In adolescents and young adults, significant impairment due to cannabis was found[89] *Executive Functioning*	*Cognitive Outcomes* Inconclusive – systematic review[93]	*Overall Neurocognitive Effect* Harm - Subgroup analyses revealed no significant differences in effect sizes by the age category (adolescents or adults)[89] *Neurocognitive Performance* Harm - Results showed that age was not a significant moderator of the relationship between cannabis use and neurocognitive performance.[95]	

	Adolescents and Young Adults	Older Adults	Stratified by Age	Stratified by Sex
	Harm - In adolescents and young adults, significant impairment due to cannabis was found for abstraction/shifting, inhibition, and updating/working memory[89] *Speed of Processing* Harm - In adolescents and young adults, significant impairment due to cannabis was found[89] *Motor Functioning* No association - In adolescents and young adults, no evidence of significant effect due to cannabis was found[89] *Verbal/Language* No association - In adolescents and young adults, no evidence of significant effect due to cannabis was found[89] *Visuospatial* No association - In adolescents and young adults, no evidence of significant effect due to cannabis was found[89]			

	Adolescents and Young Adults	Older Adults	Stratified by Age	Stratified by Sex
	Learning Harm - In adolescents and young adults, significant impairment due to cannabis was found[89]			
Prenatal Effects			*Perceptive Abilities* Inconclusive - systematic review[102] *General Cognitive Function* Inconclusive - systematic review[102] *Memory*	

	Adolescents and Young Adults	Older Adults	Stratified by Age	Stratified by Sex
			Inconclusive - systematic review[102] *Impulse Control* Inconclusive - systematic review[102] *IQ* Inconclusive - systematic review[102] *Reading Comprehension* Inconclusive - systematic review[102] *Attention* Inconclusive - systematic review[102] *Cognitive Impairment* Inconclusive - systematic review[105]	

Appendix 3: Study Characteristics

Table 6. Study Characteristics of Included Reviews

Changes to the Brain					
Author **Year** **Country**	**PICO**	**Search strategy**	**Studies included**	**Key outcomes**	**Quality Assessment**
Arnone[84] 2006 United Kingdom	*Population:* general population *Intervention:* illicit substance use *Comparator:* healthy, matched controls *Outcome:* mean diffusivity, fractional anisotropy, and intervoxel coherence changes in the corpus callosum (measures of structural damage)	*Databases searched:* BNI, CancerLit, Cochrane Library, EMBASE, Medline, PsychInfo, PubMed *Years searched:* introduction of DTI until July 2006 *Key words used:* diffusion tensor imaging, magnetic resonance imaging, DTI, RMI, alcoholism, marijuana, cannabis, cocaine, ecstasy, MDMA, methamphetamine, substance misuse *Inclusion criteria:* original data; studies that addressed the question "use of DTI in substance misuse" *Exclusion criteria:* studies that did not report significant results; studies that examine areas other than the corpus callosum	*Number of citations identified in Search:* not reported *Number of studies included:* 9 *Number of patients in all included studies:* 19	• Cannabis consumption may be associated with white matter disruption, but there is not sufficient evidence to support pathological changes in the corpus callosum	2/11
Batalla[78] 2013 Spain	*Population:* adult and adolescent *Intervention:* chronic cannabis use *Comparator:* non-users	*Databases searched:* EMBASE, Medline, PubMed, LILACS *Years searched:* inception until August 2012 *Key words used:* cannabis, marijuana, marihuana, delta-9-tetrehydrocannabinol, THC, cannabidiol, CBD, neuroimaging, brain imaging, computerized tomography, CT, magnetic	*Number of citations identified in Search:* 142	*Structural* • In adults - reduced hippocampal volume and white matter integrity in chronic users, often persisting after abstinence • In adults - changes also described in amygdala, cerebellum, and frontal cortex of chronic users • Adolescent results inconclusive	6/11

	Outcome: functional and structural changes	resonance, MRI, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, diffusion tensor MRI, DTI-MRI, spectroscopy, MRS *Inclusion criteria:* use of structural or functional neuroimaging techniques involving chronic cannabis users; inclusion of a control group of healthy volunteers matched by age, gender, and handedness; and users that were abstinent for at least 12 hours before brain scanning *Exclusion criteria:* non-neuroimaging studies of cannabis use; neuroimaging studies that involved participants who had other neurological or psychiatric disorders, or individuals who met criteria for alcohol dependence or other substance use disorders; neuroimaging studies with recreational or naïve cannabis users	*Number of studies included:* 43 *Number of patients in all included studies:* 711	*Functional* • Lower resting blood flow globally, and in cerebellum, prefrontal cortex, and striatum • No significant difference in performance between controls and users	
Batalla[79] 2014 Spain	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users *Outcome:* acute effects of brain functioning	*Databases searched:* EMBASE, Medline, PubMed, LILACS *Years searched:* inception until June 2012 *Key words used: for humans:* cannabis, marijuana, delta-9-tetrehydrocannabinol, THC, cannabidiol, CBD, cannabinoid, neuroimaging, brain imaging, magnetic resonance, MRI, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, spectroscopy, MRS; *for animals:* animal, rat, cannabis, marijuana, delta-9-tetrehydrocannabinol, THC, cannabidiol, CBD, cannabinoid, cerebral blood flow, cerebral glucose utilization, microdialysis, electrophysiological, dopamine release, single photon emission tomography, SPECT, positron emission tomography, PET *Inclusion criteria:* use of functional neuroimaging techniques involving animals naïve to cannabinoids or naïve/occasional users; acute experimental administration of cannabinoids; same gender, age, handedness in all subjects; in vivo studies involving cannabinoid effects on blood flow, cerebral metabolism, or dopamine release *Exclusion criteria:* non-neuroimaging studies of experimental administration of cannabinoids; neuroimaging studies that involved participants who had other neurological or psychiatric disorders, or individuals with substance abuse disorders; neuroimaging studies with chronic	*Number of citations identified in Search:* 224 *Number of studies included:* 45 *Number of patients in all included studies:* 889	• Increased cerebral blood flow to prefrontal, insular, cerebellar, and anterior cingulate regions; associated with depersonalization and increase anxiety • THC influenced learning, memory, and affect; CBD seems to have the opposite effect	5/11

		cannabis users; in vitro experiments; chronic or combined drug administration; anesthetized animals during the experimental procedure			
Blithikioti[82] 2019 Spain	*Population:* human *Intervention:* cannabis use (abstinence of less than 5 days) *Comparator:* non-users (abstinence of 5 days or more) *Outcome:* brain abnormalities on the cerebellum, resting cerebellar function, attention	*Databases searched:* PubMed, Science Direct, Scopus *Years searched:* inception to March 2018 *Key words used:* cannabis, marihuana, marijuana, delta 9-tetrahydrocannabinol, hashish, cerebellum *Inclusion criteria:* (1) neuroimaging and behavioral studies that included the cerebellum on the neuroimaging analysis or measured cerebellar-dependent functions, (2) studies that described the cannabis use pattern of participants (acute or chronic; and for chronic users, duration and/or pattern of consumption), (3) studies that reported the pre-study abstinence period (this criterion was applied to all studies except for structural neuroimaging studies where this criterion is not relevant), and (4) studies that included a comparison group of healthy controls (placebo-controlled trials with a within-subject design for acute effects were also included); (5) English-only *Exclusion criteria:* (1) animal studies, (2) studies with participants with psychiatric or neurological comorbidities or substance use disorders other than cannabis and/or nicotine, and (3) studies that used synthetic cannabinoids or medicinal marijuana.	*Number of citations identified in Search:* 348 *Number of studies included:* 40 *Number of patients in all included studies:* not reported	• The most consistent findings include (1) increases in cerebellar gray matter volume after chronic cannabis use, (2) alteration of cerebellar resting state activity after acute or chronic use, and (3) deficits in memory, decision making, and associative learning. Age of onset and higher exposure to cannabis use were frequently associated with increased cannabis induced alterations • Chronic cannabis use is associated with alterations in cerebellar structure and function, as well as with deficits in behavioral paradigms that involve the cerebellum (eg, eyeblink conditioning, memory, and decision making).	5/11
Colizzi[126] 2016 United Kingdom	*Population:* general human population and animals *Intervention:* cannabis and delta-9-tetrehydrocannabinol exposure *Comparator:* non-users	*Databases searched:* Medline, EMBASE, PsychInfo *Years searched:* inception until October 29th, 2015 *Key words used:* cannabis, delta-9-tetrehydrocannabinol, marijuana, marihuana, tetrahydrocannabinol, dronabinol, glu*, glutamate(s), glutamine, glutamic acid	*Number of citations identified in Search:* 268 *Number of studies included:* 41 (5 human, 36 animal)	• Chronic cannabis use associated with decreased levels of glutamate in the cortical and subcortical areas, especially in females • Delta-9-tetrehydrocannabinol affects glutamate release and reuptake and reduces the inhibition of glutamate	7/11

	Outcome: glutamate functioning	*Inclusion criteria:* human or animal studies; studies investigating the acute and/or long-term effects of cannabis use/administration or delta-9-tetrehydrocannabinol use/administration; studies measuring molecular markers related to glutamate neurotransmission including glutamate metabolites, synaptic transmission, enzyme activity, neurotransmitter release and uptake, transporters, receptors, brain neurotransmitter levels *Exclusion criteria:* studies where cannabis or delta-9-tetrehydrocannabinol were not the intervention or exposure of interest; studies in which the neurochemical outcomes were not directly reported upon	*Number of patients in all included studies:* 239 humans, animal not reported		
Cookey[83] 2014 Canada	*Population:* general population *Intervention:* cannabis use *Comparator:* early-phase schizophrenia without cannabis use vs. cannabis use without schizophrenia vs. concurrent cannabis use and schizophrenia *Outcome:* white matter tissue	*Databases searched:* Medline, EMBASE, Cochrane, PsychInfo *Years searched:* 1994 until November 2013 *Key words used:* schizophrenia, diffusion tensor imaging, humans, cannabis or marijuana smoking, diffusion, tensor, imaging, diffusion tensor imaging, early onset, first episode, cannabis, marijuana *Inclusion criteria:* English language; assess early phase schizophrenia relative to healthy controls; report diffusion tensor imaging, fractional anisotropy values *Exclusion criteria:* multiple illicit drug use or heavy alcohol use; sample sizes smaller than 20	*Number of citations identified in Search:* 65 *Number of studies included:* 18 *Number of patients in all included studies:* 725	• Decreased white matter in early-phase schizophrenia without cannabis use • Cannabis use caused additional white matter disruption, especially in adolescence	5/11
James[64] 2013 United Kingdom	*Population:* adolescent cannabis users *Intervention:* cannabis use *Comparator:* non-users	*Databases searched:* EMBASE, Medline, PubMed, PsychLIT, LILACS *Years searched:* inception until December 2012 *Key words used:* marijuana, cannabis, delta-9-tetrahydro- cannabinol, THC, cannabidiol, CBD, neuroimaging, brain imaging, computerized tomography, CT, magnetic resonance, MRI, single	*Number of citations identified in Search:* 141 *Number of studies included:* 24	• Cannabis use associated with memory disruptions, loss of IQ, loss of inhibition, and more compensatory brain activity in adolescents	5/11

	Outcome: loss of inhibition, IQ, memory	photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, diffusion tensor MRI, DTI- MRI, spectroscopy, MRS. *Inclusion criteria:* case-control design; healthy controls; participants under 19 *Exclusion criteria:* non-neuroimaging studies of cannabis use; participants older than 19; subjects with other neurological or psychiatric disorders or other substance abuse disorders	*Number of patients in all included studies:* 450		
Lorenzetti[87] 2019 Australia	*Population:* humans *Intervention:* cannabis use (defined as ongoing use and up to 28-day abstinence) *Comparator:* non-users *Outcome:* hippocampus brain volume	*Databases searched:* Pub-Med, Scopus, and PsycINFO *Years searched:* inception to 28 February 2018 *Key words used:* "Marijuana OR Cannabis" and "MRI OR Neuroimaging" *Inclusion criteria:* (1) peer-reviewed; (2) human samples; (3) published in English; (4) neuroanatomical assessment via T1-weighted MRI scans; (5) compared regular cannabis users (as defined by each study protocol) and non-users; (6) regular exposure to cannabis in the cannabis-using sample, which included ongoing use and up to 28-day abstinence. In the cannabis using samples, cannabis was defined as the current primary substance of regular use. *Exclusion criteria:* (1) regular use of substances other than cannabis, nicotine, or alcohol; (2) a diagnosis of a mental health disorder including substance (but not cannabis and nicotine) use disorders and alcohol dependence; and (3) cannabis-user group abstinent for > 28 days.	*Number of citations identified in Search:* 1046 *Number of studies included:* 30 *Number of patients in all included studies:* not reported	• Regular cannabis users had significantly smaller volumes of the hippocampus (SMD= 0.14, 95% CIs [0.02, 0.27]; Z = 2.29, p = 0.02, I2 = 74%) • The volumes of the hippocampus and orbitofrontal cortex were not significantly associated with cannabis duration and dosage.	5/11
Malchow[85] 2013 Germany	*Population:* schizophrenia patients *Intervention:* cannabis use	*Databases searched:* PubMed, We of Knowledge *Years searched:* inception until 2012	*Number of citations identified in Search:* 105 *Number of*	• Weak evidence that chronic cannabis use may affect brain morphology in patients with schizophrenia and those at high-risk • Inconclusive evidence that cannabis affects brain structure prior to schizophrenia or causes schizophrenia • Regular cannabis users had significantly smaller volumes of the orbitofrontal cortex {medial (SMD = 0.30, 95% CIs [0.15, 0.45]; Z = 3.89, p = 0.0001,	4/11

	Comparator: non-users *Outcome:* brain morphology, orbitofrontal cortex volume, lateral orbitofrontal cortex volume	*Key words used:* schizophrenia, psychosis, sMRI, structural imaging, cannabis, marijuana, marihuana, tetrahydrocannabinol *Inclusion criteria:* humans; English language; neuroimaging studies examining brain structure *Exclusion criteria:* not reported	*studies included:* 16 *Number of patients in all included studies:* 484	I2 = 51%). The volumes of the hippocampus and orbitofrontal cortex were not significantly associated with cannabis duration and dosage. • Regular cannabis users had significantly smaller volumes of the lateral OFC compared to controls (SMD = 0.19, 95% CIs [0.07, 0.32]; Z = 3.10, p = 0.002, I2 = 26%)}	
Martin-Santos[77] 2010 United Kingdom	*Population:* adults *Intervention:* cannabis use *Comparator:* non-users *Outcome:* blood flow, brain volume	*Databases searched:* EMBASE, Medline, PubMed, LILACS, PsychLIT, books on substance abuse neuroimaging *Years searched:* inception until January 2009 *Key words used:* marijuana, cannabis, delta-9-tetrahydrocannabinol, THC, cannabidiol, CBD, neuroimaging, brain imaging, computerized tomography, CT, magnetic resonance, MRI, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, diffusion tensor MRI, DTI-MRI, spectroscopy, MRS *Inclusion criteria: for case-control studies:* inclusion of a control group of healthy volunteers matched for age, sex, and handedness; users were abstinent for 12 hours before brain scanning; *for experimental administration of cannabinoids:* parallel or cross-over design; participants were abstinent for at least 1 week *Exclusion criteria:* non-neuroimaging studies of cannabis use; neuroimaging studies involving those under 18 years of age; subjects who had other neurological or psychiatric disorders or who tested positive for drugs other than cannabis	*Number of citations identified in Search:* 66 *Number of studies included:* 41 *Number of patients in all included studies:* 665	• Lower resting global, prefrontal, and anterior cingulate cortex blood flow in cannabis users, related to impairments in time estimation, attention, working memory, cognitive flexibility, decision making and psychomotor speed • Impaired cognitive efficiency in cannabis users compared to controls • Changes in volume only related to chronic users	5/11
Rapp[81] 2012	*Population:* psychosis or at high-risk or genetic risk of psychosis	*Databases searched:* ISI Web of Knowledge, PubMed	*Number of citations*	• Cannabis use associated with decreased activity globally and in the cingulum, dorsolateral prefrontal cortex, and cerebellum in users with or at high risk of psychosis compared to healthy non users	7/11

Switzerland	*Intervention:* cannabis uses *Comparator:* healthy, non-users *Outcome:* brain activity, white matter	*Years searched:* inception until November 2011 *Key words used:* psychosis, schizophrenia, first episode, at-risk mental state, high risk, and cannabis, marijuana, delta-9-tetrahydrocannabinol, and brain structure, neuroimaging, brain imaging, brain abnormalities, magnetic resonance, diffusion sensor MRI, post mortem, quantitative autoradiography, radiology and binding, in situ hybridization *Inclusion criteria:* original publication in a peer reviewed journal; studying the brain of psychosis patients or individuals at risk for psychosis or individuals at genetic risk for psychosis in relation to cannabis use applying in vivo structural neuroimaging or post mortem autoradiography or in situ hybridization techniques; included both cannabis smokers and non-smokers; described specific effects of cannabis on brain if subjects had a general substance abuse or substance dependence disorder diagnosis *Exclusion criteria:* functional brain imaging studies	*identified in Search:* 33 *Number of studies included:* 19 *Number of patients in all included studies:* 350	• Post mortem results and studies examining white matter changes were inconclusive	
Reece[23] 2009 Australia	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users, occasional users *Outcome:* neurodevelopment	*Databases searched:* Medline, PubMed, PsychInfo, Google Scholar, Scopus, ProQuest, Web of Knowledge, EbscoHost *Years searched:* not reported *Key words used:* cannabis, marijuana, marihuana, toxicity, complications, mechanisms *Inclusion criteria:* original data; describe mechanisms; published in “recent years” *Exclusion criteria:* not reported	*Number of citations identified in Search:* 5198 *Number of studies included:* not reported *Number of patients in all included studies:* not reported	• Chronic cannabis use associated with worsening psychotic symptoms, violent suicides, higher anxiety, increased inflammation in lungs, and can cause cardiovascular issues • Heavy chronic use may be associated with bone loss and certain cancers	2/11
Nader[80]	*Population:* adults ≥18 years old	*Databases searched:* PubMed, LILACS, SciELO	*Number of citations*	• The neuropsychological studies provide evidence for subtle cognitive deficits at least 7 days after heavy cannabis use. The structural neuroimaging studies show growing evidence of abnormalities in	4/11

2018 Brazil	*Intervention:* regular cannabis use *Comparator:* not reported *Outcome:* functional brain abnormalities, structural brain abnormalities	*Years searched:* January 2010 to August 2016 *Key words used:* "cannabis" OR "marijuana" AND "cognitive effects" OR "brain imaging" *Inclusion criteria:* (i) original studies that investigated the effects of regular cannabis use on cognition, brain structure and function employing neuropsychological tests and the following neuroimaging techniques: magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET); (ii) studies that compared a group of cannabis users whose principal drug of abuse was cannabis used on a regular basis (as defined by each study protocol) with a group of controls; and (iii) studies with adults (≥18 years); English, Spanish, or Portuguese *Exclusion criteria:* (i) animal studies; (ii) studies among adolescents (< 18 years); (iii) samples with specific neurological or psychiatric disorders; (iv) studies among subjects with any substance use disorder other than cannabis; (v) studies that evaluated medical use of cannabis or cannabinoids; (vi) studies that addressed acute effects only; (vii) studies that focused on neurochemical, genetic or other aspects of cannabis use; and (viii) review articles	*identified in Search:* 713 *Number of studies included:* 56 *Number of patients in all included studies:* not reported	hippocampus volume and gray matter density of cannabis users relative to controls; however, morphological changes in other brain regions are more controversial. The functional neuroimaging studies suggest an altered pattern of brain activity associated with cannabis use. •	
Rocchetti[86] 2013 United Kingdom	*Population:* non-psychotic population *Intervention:* cannabis use *Comparator:* non-users *Outcome:* hippocampal volume, amygdala volume, whole brain volume	*Databases searched:* Web of Knowledge (Medline, Web of Science) *Years searched:* inception to February 2013 *Key words used:* MRI, DTI, VBM, cannabis, neuroimaging, structural, grey matter, white matter *Inclusion criteria:* original paper or short communication in a peer-reviewed journal; recruited cannabis-user subjects without a diagnosis of psychosis and matched controls; employed structural imaging techniques; reported sufficient data to allow meta-analytical computations	*Number of citations identified in Search:* not reported *Number of studies included:* 14 *Number of patients in all included studies:* 362	• No statistically significant differences in whole brain volume between users and non-users • Significantly decreased hippocampal volume in users • Inconsistent results on amygdala volume due to publication bias	8/11

		Exclusion criteria: subjects with a diagnosis of a psychotic disorder; overlapping samples; systematic or critical reviews; did not report enough data to be included in the meta-analysis			
Sami[127] 2015 United Kingdom	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users *Outcome:* dopamine functioning	*Databases searched:* Medline, EMBASE, PsychInfo *Years searched:* inception until July 2014 *Key words used:* cannabidiol, cannabinoid, cannabis, CBD, THC, hashish, marijuana, tetrahydrocannabinol, endocannabinoid, dopa*, dopamine, PHNO, raclopride, fallypride, iodobenzamide, IBZM, FMT, PE21, CIT, NNC112, SCH23390, D1, D2, D3, DAT, AADC, MAO *Inclusion criteria:* human studies; investigating acute and long-term effects of cannabinoid administration; measuring molecular markers related to dopaminergic neurotransmission including biomarkers in peripheral blood, in vivo imaging, or post mortem brain tissue *Exclusion criteria:* studies where cannabinoid administration was not the intervention or exposure of interest; or where neurochemical outcomes were not directly reported on	*Number of citations identified in Search:* 2796 *Number of studies included:* 25 *Number of patients in all included studies:* 244	• Minimal evidence, but acute cannabis use is weakly associated with increased peripheral and striatal dopamine and decreased neocortical dopamine • Similar results for chronic users • Larger effects in those at genetically predisposed to or at clinical high risk of psychosis	6/11
Sneider[76] 2014 United States	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users *Outcome:* brain chemistry	*Databases searched:* PubMed, EMBASE *Years searched:* not reported *Key words used:* marijuana, cannabis, MRS, MRSI, proton MRS *Inclusion criteria:* not reported *Exclusion criteria:* neuroimaging other than MRS (MRI, CT, PET, DTI, fMRI, CBF, CBV)	*Number of citations identified in Search:* not reported *Number of studies included:* 8 *Number of patients in all*	• Cannabis use associated with lower levels of N-acetyl-aspartate, myo-inositol, and choline, which are associated with lower cognitive efficiency and impulse control • Associated with alterations in GABA levels in the frontal lobe	1/11

			included studies: 140		
Cancer					
Author **Year** **Country**	**PICO**	**Search strategy**	**Studies included**	**Key outcomes**	**Quality Assessment**
De Carvalho[72] 2015 Brazil	*Population:* adult *Intervention:* cannabis use *Comparator:* non-users *Outcome:* head and neck cancer	*Databases searched:* the Cochrane library, PubMed, LILACS, EMBASE, BBO, Bireme SciELO *Years searched:* inception to July 2015 *Key words used:* hashish, marijuana, bhang, ganja, hemp, C. *sativa*, oral, oropharyngeal, nasopharyngeal, head and neck neoplasms, neoplasm neck, cancer of the head and neck, head and neck cancer, head cancer, neck cancer, aerodigestive tract neoplasms upper, upper aerodigestive tract neoplasms *Inclusion criteria:* case-control studies, cohort, or systematic reviews; allocation criteria defined for cases and controls; cases with definitive diagnosis of head and neck cancer; matched controls by at least gender *Exclusion criteria:* technical articles; reports or case reports; opinion articles; review articles	*Number of citations identified in Search:* 3558 *Number of studies included:* 6 *Number of patients in all included studies:* 907	• No association between lifetime cannabis use and risk of head and neck cancer (OR = 1.021, 95% CI = 0.912-1.143)	9/11
Ghasemiesfe[71] 2019 United States	*Population:* adults *Intervention:* cannabis use (≥1 joint-year exposure)	*Databases searched:* PubMed, Embase, PsycINFO, MEDLINE, and the Cochrane Library *Years searched:* January 1973 to April 2019	*Number of citations identified in Search:* 2251 *Number of studies included:* 25	• In pooled analysis of case-control studies, ever use of marijuanawas not associated with head and neck squamous cell carcinoma or oral cancer. • In pooled analysis of 3 case-control studies, more than 10 years of marijuana use (joint-years not reported) was associated with TGCT (OR, 1.36; 95%CI, 1.03-1.81; P = .03; I2 = 0%) and nonseminoma TGCT (OR, 1.85; 95%CI, 1.10-3.11; P = .04; I2 = 0%). • Evaluations of ever use generally found no association with cancers, but exposure levels were low and poorly defined. Findings for lung cancer	10/11

	Comparator: non-users *Outcome:* lung, oral cancer, other cancers, testicular germ cell tumor, testicular, seminoma testicular germ cell tumor, non-seminoma testicular germ cell tumor, urogenital cancer, head and Neck Squamous Cell Carcinoma (ever use) in case-control studies	*Key words used:* marijuana OR marihuana OR tetrahydrocannabinol OR cannabinoid OR cannabis; AND cancer OR malignancy OR carcinoma OR tumor OR neoplasm *Inclusion criteria:* studies published in English involving participants 18 years or older with at least 1 joint-year exposure (equivalent of 1 joint per day for 1 year) or more cumulative use (defined as ever use) of marijuana and reporting on the development of cancer *Exclusion criteria:* review articles, commentaries, case reports, case series, editorial articles, in vitro and animal studies, studies that did not primarily evaluate marijuana exposure or include information on cancer outcomes, studies that reported only outcomes after short-term exposure in a laboratory setting, and studies that included fewer than 10 marijuana users	*Number of patients in all included studies:* not reported	were mixed, confounded by few marijuana-only smokers, poor exposure assessment, and inadequate adjustment	
Gurney[73] 2015 New Zealand	*Population:* adult males *Intervention:* cannabis use *Comparator:* non-users *Outcome:* testicular	*Databases searched:* CINAHL, Cochrane library, EMBASE, Medline, ProQuest Central, ProQuest Dissertations and Theses, Scopus, Web of Science *Years searched:* January 1980 until May 2015 *Key words used:* cannabi*, marijuana, marihuana, THC, tetrahydrocannabinol, cancer of the testi*, seminoma*, testi* cancer, testi* carcinoma, testi* germ cell tumo(u)r, testi* neoplasm, testi* tumo(u)r *Inclusion criteria:* reported association between cannabis and testicular cancer; data provided were summary associations *Exclusion criteria:* not reported	*Number of citations identified in Search:* 149 *Number of studies included:* 3 *Number of patients in all included studies:* 719	• Current cannabis use, using cannabis on a weekly basis, and chronic use associated with testicular germ cell tumors • Current cannabis use: OR = 1.62 (95% CI = 1.13-2.31) • Weekly use: OR = 1.92 (95% CI = 1.35-2.72) • Chronic use (more than 10 years): OR = 1.50 (95% CI = 1.08-2.09)	8/11
Huang[70]	*Population:* general population	*Databases searched:* PubMed, Medline	*Number of citations identified in*	• No association with head and neck, and lung cancer • Associated with testicular cancer	5/11

2015 United States	*Intervention:* cannabis use *Comparator:* non-users *Outcome:* bladder, cervical, head and neck, lung, childhood cancers, penile, prostate, testicular	*Years searched:* inception until August 2014 *Key words used:* marijuana, cannabis, cancer *Inclusion criteria:* epidemiologic studies investigating cannabis use that provided risk estimates for cannabis exposure *Exclusion criteria:* not reported	*Search:* not reported *Number of studies included:* 34 *Number of patients in all included studies:* 21,138	• Insufficient evidence for bladder, prostate, penile, cervical and childhood cancer, but small associations exist for prostate and cervical cancer • Tends to be dose-dependent	
Martinasek[37] 2016 United States	*Population:* human *Intervention:* cannabis use (inhalational marijuana) *Comparator:* not reported *Outcome:* lung cancer	*Databases searched:* PubMed, OVID, Web of Science *Years searched:* 1967 to 2015 *Key words used:* advanced term “Marijuana", Marijuana smoking and respiratory system, Cannabis: adverse effects, Marijuana smoking: epidemiology, Marijuana smoking/epidemiology, Cannabis/adverse effects*, Marijuana smoking/epidemiology*, Marijuana smoking/physiopathology, Lung diseases/chemically induced, Marijuana smoking/adverse effects*, Respiratory system/drug effects*, Marijuana abuse/respiratory complications *Inclusion criteria:* studies focusing on respiratory health effects of inhalational marijuana *Exclusion criteria:* duplicates, systematic reviews, editorials, commentaries, letters, reviews, non-English language articles, animal studies, unattainable full text articles, or those that were not inclusive of respiratory health	*Number of citations identified in Search:* 281 *Number of studies included:* 48 *Number of patients in all included studies:* not reported	• The research indicates that there is a risk of lung cancer from inhalational marijuana as well as an association between inhalational marijuana and spontaneous pneumothorax, bullous emphysema, or COPD. • A variety of symptoms have been reported by inhalational marijuana smokers, including wheezing, shortness of breath, altered pulmonary function tests, cough, phlegm production, bronchodilation, and other symptoms.	4/11
Mehra[69]	*Population:* general population	*Databases searched:* Medline, EMBASE, Psychlit	*Number of citations*	• Cannabis smoking associated with more inhaled tar exposure than tobacco smoking • More pathological lung changes in cannabis smokers compared to tobacco smokers	8/11

2006 United States	*Intervention:* cannabis smoking *Comparator:* non-users, tobacco-only smokers *Outcome:* lung cancer	*Years searched:* 1966 until October 2005 *Key words used:* cannabis, cannabinoids, marijuana abuse, marijuana smoking, marijuana usage, neoplasms, carcinoma, pathology, smoking/pathology, tars/respiratory tract diseases, respiratory physiology, lung, respiratory tract tumor, respiratory tract infections, respiratory system *Inclusion criteria:* adults (18+); humans *Exclusion criteria:* letters, reviews, case series involving fewer than 10 patients; studies not involving humans or intentional smoking or lung conditions	*identified in Search:* 186 *Number of studies included:* 19 *Number of patients in all included studies:* 66,349 (only the number of male participants reported)	• No association with cannabis smoking and lung cancer, despite more tar and pathological changes	
Rajanahally[38] 2019 United States	*Population:* male *Intervention:* marijuana use *Comparator:* not reported *Outcome:* urologic malignancies	*Databases searched:* Medline, Embase *Years searched:* inception to May 2017 *Key words used:* 'marijuana', 'cannabis', 'cannabinoids', 'endocannabinoids', 'infertility' (male), 'semen analysis', 'hypogonadism', 'testosterone', 'gonadotropins', 'libido', 'erectile dysfunction', 'testicular cancer', 'germ cell tumor', 'prostate cancer', 'penile cancer', 'bladder cancer', 'kidney cancer', 'renal carcinoma' *Inclusion criteria:* English studies; vitro models, case series, case–control, cohort designs *Exclusion criteria:* not human, in vitro, or mammalian species; review articles	*Number of citations identified in Search:* 1897 *Number of studies included:* 30 *Number of patients in all included studies:* not reported	• Overall, cannabis consumption has a negative impact on fertility using semen parameters as a surrogate. • There did not appear to be a significant relationship between long-term cannabis consumption and the HPG axis hormones in the clinical studies. • Marijuana consumption appears to be an independent risk factor for the development of testicular germ cell tumors. •	4/11
Song[74] 2020	*Population:* adolescent and young adult men	*Databases searched:* PubMed, Scopus, Web of Science	*Number of citations identified in Search:* 338	• Asociation of marijuana use with nonseminoma, summary odds ratio [sOR] = 1.71 (95% confidence interval [CI] 1.12−2.60)	4/11

United States	*Intervention:* marijuana use *Comparator:* no marijuana use *Outcome:* nonseminomatous testicular germ cell tumors	*Years searched:* inception to January 31, 2020 *Key words used:* reported in supplementary *Inclusion criteria:* (1) testicular cancer, and (2) participants' history of either marijuana use or tobacco smoking (3) used incident TGCT as the outcome variable, (4) enrolled a comparison group of cancer-free men, and (5) addressed age of participants by either design or analysis. *Exclusion criteria:* Studies without human subjects, case reports, and studies of germ cell tumors of childhood	*Number of studies included: 4* *Number of patients in all included studies:* not reported		
Health Effects					
Author **Year** **Country**	**PICO**	**Search strategy**	**Studies included**	**Key outcomes**	**Quality Assessment**
Calabria[18] 2010 Australia	*Population:* general population *Intervention:* cannabis exposure *Comparator:* not specified *Outcome:* overall mortality	*Databases searched:* Medline, EMBASE, PsychInfo *Years searched:* January 1990 until January 2008 *Key words used:* cannabis, mortality, cohort, drug use *Inclusion criteria:* human studies; mortality associated with cannabis use or dependence *Exclusion criteria:* not focused on cannabis or mortality; review articles and case series	*Number of citations identified in Search:* not reported *Number of studies included:* 19 *Number of patients in all included studies:* 387,635	• Insufficient data to determine all-cause mortality is higher in users compared to the general population • Heavy cannabis use associated with increased risk of poor driving • Cannabis use associated with suicide, but minimal evidence	5/11

			(cannabis use not reported)		
Chisini[16] 2018 Brazil	*Population:* adolescents, adults, and elderly people *Intervention:* cannabis use (marijuana and hashish) *Comparator:* non-users *Outcome:* periodontitis	*Databases searched:* PubMed, Scopus, ISI Web of Science, BVS—Virtual health library, Scielo *Years searched:* inception to Nov 2018 *Key words used:* periodontal Diseases, Gingivitis, Marijuana, Cannabis *Inclusion criteria:* comprised studies with cross-sectional and longitudinal design, studies that investigated the possible association between the use of Cannabis and periodontal disease in human populations. Any language restrictions or publication period were considered. *Exclusion criteria:* Studies with case-control design, reviews, technical reports, case reports and series, abstracts from conferences, letters to the editor and qualitative studies were excluded.	*Number of citations identified in Search:* 75 *Number of studies included:* 5 *Number of patients in all included studies:* 13491	• Positive association was observed between the use of cannabis and periodontitis (PR 1.12 CI 95% [1.06-1.19]). • The results of systematic review and meta-analyses demonstrate that the use of Cannabis is associated with a higher prevalence of periodontitis.	9/11
Colizzi[27] 2018 United Kingdom	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users, occasional users *Outcome:* behavioural measures, physiological measures	*Databases searched:* MEDLINE, Web of Science and Scopus *Years searched:* Inception (assumed) to June 2018 *Key words used:* (“marijuana”, “cannabis”, “THC/ delta-9-tetrahydrocannabinol/dronabinol”), its pattern of use (“heavy”, “regular”, “frequent”, “light”, “non-regular”, “occasional”), the study design (“acute”, “challenge”, “administration”), and the outcome of interest (“tolerance”, “sensitization”), *Inclusion criteria:* (1) human studies, (2) studies investigating the impact of a single administration of Δ9-THC or cannabis in 2 or more populations with different levels of previous	*Number of citations identified in Search:* 1252 *Number of studies included:* 36 *Number of patients in all included studies:* 1047	• Research evidence tends to suggest that the acute effects of single cannabinoid administration are less prominent in regular cannabis users compared to non-regular users. • Studies of repeated cannabinoid administration more consistently suggest less prominent effects upon repeated exposure. Cognitive function is the domain showing the highest degree of tolerance, with some evidence of complete absence of acute effect (full tolerance). The acute intoxicating, psychotomimetic, and cardiac effects are also blunted upon regular exposure, but to a lesser extent (partial tolerance). Limited research also suggests development of tolerance to other behavioral, physiological, and neural effects of cannabis.	6/11

		cannabis exposure (i.e. frequent users, occasional users, naïve individuals), (3) studies investigating the impact of a single administration of Δ9-THC or cannabis in a single population with variation in the extent of previous cannabis exposure (i.e. correlating the acute effect of Δ9-THC or cannabis on the outcome measure with the extent of previous cannabis exposure), or (4) studies investigating the impact of repeated administration of Δ9-THC or cannabis in population(s) of cannabis users (i.e. (re)assessing the outcome measure after every administration). *Exclusion criteria:* (1) studies where the effects of Δ9-THC or cannabis were not investigated under experimental conditions, (2) studies in which groups were not differentiated in terms of previous cannabis exposure, (3) studies which primarily assessed the effects of psychoactive substances other than cannabis, and (4) studies which primarily/ exclusively assessed cannabinoid pharmacokinetics without investigating other outcomes of interest			
Farooqui[36] 2019 United States	*Population:* Hepatic fibrosis in patients over the age of 16 with chronic liver disease *Intervention:* cannabis use (cannabis smoking) *Comparator:* No smoking of cannabis *Outcome:* progression of hepatic fibrosis in Hepatitis C patients, progression of hepatic fibrosis, hepatic steatosis	*Databases searched:* Medline, EMBASE, Cochrane databases, and Web of Science *Years searched:* Inception to January 2018 *Key words used:* cannabis; cirrhosis; hepatic fibrosis; marijuana *Inclusion criteria:* observational in nature or evaluated prevalence and/or progression of hepatic fibrosis in patients with chronic liver disease who smoked or did not smoke marijuana. All etiologies of chronic liver disease were included in the study. We restricted the inclusion criteria to studies with patients greater than 16 years of age. We included only fully published and peer-reviewed studies. *Exclusion criteria:* unpublished data	*Number of citations identified in Search:* 7099 *Number of studies included: 9* *Number of patients in all included studies:* not reported	• Pooled OR for prevalence of fibrosis was 0.91 (0.72–1.15), I2 = 75%. • On subgroup analysis, pooled OR among non-alcoholic fatty liver disease patients was 0.80 (0.75–0.86), I2 = 0% and pooled OR among Hepatitis C (HCV) patients was 1.96 (0.78–4.92), I2 = 77%. • Among studies evaluating HR, pooled HR for progression of fibrosis in HCV–HIV coinfected patients was 1.03 (0.96–1.11), I2 = 0%. • Pooled OR with 95% CI for prevalence of steatosis in marijuana users vs non-users was 0.80 (0.75–0.85), Cochran's Q-test, P = 0.48, I2 = 0%.	8/11
French[35] 2019 United Kingdom	*Population:* adults aged ≥16 years *Intervention:* cannabis use	*Databases searched:* Medline,Embase and PsycInfo, World Health Organization website, Google Scholar	*Number of citations identified in Search:* 373	• Study designs were heterogeneous. Six studies utilized relevant comparator group. Four of these investigated the association between cannabis use and latent TB infection; all provided some evidence of an association, although only two of these had adjusted for confounders.	9/11

	Comparator: non-users *Outcome:* Tuberculosis (latent of active)	*Years searched:* Inception to January 2018 *Key words used:* Tuberculosis, Cannabis, Systematic review, Evidence synthesis *Inclusion criteria:* All types of primary epidemiological studies (e.g. descriptive studies, outbreak reports, cohort studies, case-control studies); Population: adults aged ≥16 years; Exposure: cannabis use by any means; Comparator: any e.g. no reported cannabis use, no comparator; Outcome: active TB disease affecting any clinical site (pulmonary or extra-pulmonary) or latent infection e.g. assessed by Tuberculin Skin Testing [TST] ('Mantoux' test) or an interferon-gamma release assay. *Exclusion criteria:* not reported	*Number of studies included: 11* *Number of patients in all included studies:* not reported	• The remaining two comparator studies investigated the association between cannabis use and active TB disease; neither found evidence of an association after adjusting for confounding. • All six studies were at "Serious" risk of bias. The five studies, which did not utilize a relevant comparator group, were all indicative of TB outbreaks occurring among cannabis users, but the quality of the evidence was very weak.	
Gates[128] 2014 Australia	*Population:* general population *Intervention:* measured cannabis *Comparator:* non-users *Outcome:* sleep	*Databases searched:* EMBASE, CINAHL, Cochrane Library/EBM Reviews, Medline, PsycEXTRA *Years searched:* inception until 2012 *Key words used:* cannabinoid/s, tetrahydrocannabinol, THC, cannabis/marijuana, sleep, sleep onset, sleep apnea, sleep treatment, sleep wake cycle, sleep deprivation, rapid eye movement (REM) sleep, non-rapid eye movement (NREM) sleep, sleep disorder, insomnia *Inclusion criteria:* not reported *Exclusion criteria:* review papers, posters, qualitative articles, opinion pieces, letter, editorials, case reports (n<7), published abstracts	*Number of citations identified in Search:* 2215 *Number of studies included:* 39 *Number of patients in all included studies:* 203 recreational users	• No consistent effect of cannabis on sleep time • Increased time spent in stage 2 and decreased time in slow wave sleep • Overall results inconsistent	4/11
Ghasemiesfe[32]	*Population:* participants older than 12 years	*Databases searched:* PubMed, Embase, PsycINFO, MEDLINE, and the Cochrane Library	*Number of citations*	• Our review suggests that use (more than once per week for at least 1 year) is associated with cough, sputum production, and wheezing.	8/11

2018 United States	*Intervention:* cannabis use (at least 30 days of lifetime marijuana use) *Comparator:* non-users *Outcome:* cough, in prospective cohort studies, Chronic bronchitis, in cross-sectional studies, Obstructive lung disease Pulmonary function: FEV1, Pulmonary Function: FVC, Pulmonary Function: FEV1 - FVC ratio, Pulmonary Function: Airway resistance and specific conductance of airways, Pulmonary Function: Other respiratory outcomes, Sputum production, in prospective cohort studies Cough, in cross-sectional studies, Sputum production, in cross-secitonal studies, Wheezing, in cross-sectional studies, Dyspnea, in cross-sectional studies	*Years searched:* January 1, 1973 to April 30, 2018 *Key words used:* marijuana and respiratory terms *Inclusion criteria:* observational (cohort, case-control, and cross-sectional) and interventional studies (randomized controlled and experimental) studies that were published in Englished and involved participants older than 12 years who had at least 30 days of lifetime marijuana use *Exclusion criteria:* studies reporting only outcomes after short-term exposure in a laboratory setting and those including fewer than 10 marijuana users.	*identified in Search:* 927 *Number of studies included:* 22 *Number of patients in all included studies:* not reported	• Evidence on the association between daily use and obstructive lung disease and impaired pulmonary function testing is insufficient.	
Goldenberg[31] 2017 United States	*Population:* recreational cannabis users *Intervention:* recreational cannabis use *Comparator:* non-users	*Databases searched:* Pubmed, CINAHL, PsychInfo, Cochrane Library of Controlled Trials, and Cochrane Library of Systematic Reviews *Years searched:* "Through 2015" *Key words used:* quality of Life, Cannabis	*Number of citations identified in Search:* 207 *Number of studies included:* 14 *Number of patients in all*	• Fourteen studies met our pre-defined selection criteria. The studies were heterogeneous and their quality was low. • With one exception, we did not identify any population for whom cannabis use was associated with improved QoL. QoL was lower in persons who used cannabis heavily, or who met criteria for CUD. However, this association was inconsistent and the magnitude was weaker than the relationship between QoL and use of other addictive substances (including tobacco and illicit drugs).	2/11

	Outcome: quality of Life/Health Related Quality of Life	*Inclusion criteria:* Articles in English or with an available English translation; publication in a peer-reviewed journal; focusing on cannabis or synthetic cannabinoids; measured quality of life or health-related quality of life using a generic or disease-specific multi-item questionnaire; reported an outcome related to global quality of life/health related quality of life or domain scores *Exclusion criteria:* not being available in English or in English translation; being poster/presentation synopses and not full-text articles; not specifically relating the quality of life results to cannabis use; and for not utilizing a validated and widely used generic or disease specific quality of life scale; cannabis as a medical treatment or cannabis that was administered as a pharmaceutical preparation.	*included studies:* not reported		
Grotenhermen[19] 2010 Germany	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users *Outcome:* arteritis	*Databases searched:* PubMed, EMBASE, Web of Science *Years searched:* inception until February 2009 *Key words used:* cannabi*, marijuana, THC, arteritis, thromboangiitis obliterans, Buerger's disease *Inclusion criteria:* case reports, reviews, commentaries; cannabis arteritis; TAO mentioning cannabis, cannabis, cannabinoids, or THC *Exclusion criteria:* not reported	*Number of citations identified in Search:* not reported *Number of studies included:* 17 *Number of patients in all included studies:* 94	• Most studies had concurrent tobacco and cannabis use, so little association was found for just cannabis and arteritis	4/11
Hackam[26] 2015 Canada	*Population:* patients suffering from stroke *Intervention:* cannabis exposure *Comparator:* non-users	*Databases searched:* Medline, EMBASE *Years searched:* inception until November 30th, 2014 *Key words used:* cannabis, cerebrovascular disease	*Number of citations identified in Search:* 989 *Number of studies included:* 34	• Cannabis exposure associated with increased risk of stroke	5/11

	Outcome: stroke	*Inclusion criteria:* case studies; cases underwent parenchymal imaging; humans *Exclusion criteria:* not reported	*Number of patients in all included studies:* 64		
Jouanjus[22] 2017 United States	*Population:* subjects using cannabis based products and suffering from any cardiovascular disease, without any distinction of age, gender, or nationality *Intervention:* cannabis-based products (defined as the plant Cannabis sativa in its different forms, synthetic cannabinoids, and cannabis-derived prescription drug; exposure (identified by self-report or positive toxicological analyses) could be acute or chronic, motivated by recreational or therapeutic purposes, and using any mode of administration *Comparator:* not reported *Outcome:* cardiovascular risk, coagulation, myocardial infarction, electrocardiographic abnormalities, cerebrovascular disease	*Databases searched:* Cochrane Database of Systematic Review (CDSR), the Cochrane Central Register of Controlled Trials (CENTRAL), the Web of Science, PubMed *Years searched:* January 1, 2016 to May 31, 2016 *Key words used:* (Cardiovascular Disease OR Cardiac Disease OR Heart Disease OR Vascular Disease OR Stroke OR Myocardial* OR Acute Coronary Syndrome OR Tachycardia Or Hypertension OR*carditis OR Stenosis OR Arrhythmias OR Cardiac Arrest OR Aneurysm OR Hypotension OR Vasculitis OR Hyperemia OR Cerebrovascular OR Thrombosis OR Embolism OR Heart Failure OR Aortic Disease OR Heart Arrest OR Tamponade OR Cardiomegaly OR Cardiomyopathy OR Fibrillation OR Angor OR Heart Rupture OR Tricuspid Or Mitral OR Cardiac Ischemia Or Ventricular Dysfunction OR Angiodysplasia OR Angioedema OR Angiopathy OR Superior Vena Cava Syndrome OR Telangiectasis OR Varicocele OR Vasoplegia OR Vascular Fistula OR Venous Insufficiency OR Bradycardia OR Atherosclerosis OR Arteriopathy) AND (Cannabis OR Marijuana Abuse OR Marijuana Smoking OR Cannabinoids OR Hashish OR Hemp OR Bhang OR Marijuana OR Ganja) *Inclusion criteria:* no restriction on the design; experimental studies were eligible for inclusion as long as conducted on human cells or tissues; all types of original articles; references of eligible reviews were screened to search for articles meeting review criteria *Exclusion criteria:* animals, including those using animal cells or tissues; did not assess the adverse cardiovascular effects of cannabis or focused on endocannabinoids; meeting abstracts, letters to editors, editorials, and comments were excluded, unless they presented well-documented new data (this concerned case reports only)	*Number of citations identified in Search:* 826 *Number of studies included:* 115 *Number of patients in all included studies:* not reported	• Evidenced an association between exposure to cannabis-based products and cardiovascular disease. • Currently, this evidence is stronger for ischemic strokes than for any other cardiovascular diseases. While the data are limited, there is some suggestion that cannabis use may have negative cardiovascular consequences, particularly at large doses. • Overall, the data reporting an association between cannabis exposure and myocardial infarction is weaker than that related to strokes. • Evidence on the impact of cannabis use on heart rhythm is limited. • The impact of cannabis-based consumption on coagulation has not been clearly elucidated.	3/11

Kennedy[34] 2017 Australia	*Population:* patients with exertional angina who were not regular users of cannabis *Intervention:* 2% THC smoked from 500 mg marijuana cigarettes *Comparator:* placebo; isoproterenol 2 mL of 0.5% *Outcome:* exercise-induced asthma	*Databases searched:* Pubmed, Medline, Embase *Years searched:* not reported *Key words used:* cannabis, marijuana, cannabinoids and THC, in sport and exercise *Inclusion criteria:* Only English language literature was reviewed and included only articles that specified the details of a formal exercise program or protocol. Individuals in rehabilitationor health screening programs involving exercise were included as the study may have identified adverse reactions in the marijuana group *Exclusion criteria:* Review articles, opinion pieces, policy statements by sporting bodies and regulatory agencies were excluded	*Number of citations identified in Search:* not reported *Number of studies included:* 1 *Number of patients in all included studies:* 8	• THC caused prompt reversal of exercise and methacholine induced bronchospasm	2/11
Koranztopolous[24] 2008 Greece	*Population:* participants with atrial fibrillation *Intervention:* cannabis smoking *Comparator:* non-smokers *Outcome:* atrial fibrillation	*Databases searched:* Medline, EMBASE *Years searched:* inception until January 2007 *Key words used:* marijuana, hashish, cannabis, atrial fibrillation, arrhythmias, tachycardia, palpitations, heart, cardiovascular *Inclusion criteria:* not reported *Exclusion criteria:* not reported	*Number of citations identified in Search:* not reported *Number of studies included:* 6 *Number of patients in all included studies:* 6	• Cannabis smoking associated with atrial fibrillation, but minimal evidence exists	4/11
Martinasek[37]	*Population:* human	*Databases searched:* PubMed, OVID, Web of Science	*Number of citations*	• The research indicates that there is a risk of lung cancer from inhalational marijuana as well as an association between inhalational marijuana and spontaneous	4/11

2016 United States	*Intervention:* cannabis use (inhalational marijuana) *Comparator:* not reported *Outcome:* COPD, respiratory symptoms, spontaneous pneumothorax, bullous empysema	*Years searched:* 1967 to 2015 *Key words used:* advanced term “Marijuana", Marijuana smoking and respiratory system, Cannabis: adverse effects, Marijuana smoking: epidemiology, Marijuana smoking/epidemiology, Cannabis/adverse effects*, Marijuana smoking/epidemiology*, Marijuana smoking/physiopathology, Lung diseases/chemically induced, Marijuana smoking/adverse effects*, Respiratory system/drug effects*, Marijuana abuse/respiratory complications *Inclusion criteria:* studies focusing on respiratory health effects of inhalational marijuana *Exclusion criteria:* duplicates, systematic reviews, editorials, commentaries, letters, reviews, non-English language articles, animal studies, unattainable full text articles, or those that were not inclusive of respiratory health	*identified in Search:* 281 *Number of studies included:* 48 *Number of patients in all included studies:* not reported	pneumothorax, bullous emphysema, or COPD. • A variety of symptoms have been reported by inhalational marijuana smokers, including wheezing, shortness of breath, altered pulmonary function tests, cough, phlegm production, bronchodilation, and other symptoms.	
Meehan-Atrash[30] 2019 United States	*Population:* humans ≥18 years old *Intervention:* inhalational marijuana *Comparator:* not reported *Outcome:* laryngeal symptoms, lung function, respiratory problems	*Databases searched:* MEDLINE via PubMed, CINAHL, Scopus, Cochrane Library *Years searched:* January 1, 2007 to August 10, 2018 *Key words used:* marijuana, cannabis, respiratory, lungs, larynx,voice, phonation, vocal *Inclusion criteria:* observational and interventional studies; clinical or animal research *Exclusion criteria*: participants younger than 18 years; studies in a language other than English; case reports	*Number of citations identified in Search:* 709 *Number of studies included:* 6 *Number of patients in all included studies:* not reported	• The only study to date that has evaluated the association between laryngeal symptoms and inhaling cannabis found that human smokers assessed by indirect laryngoscopy with mirror examination exhibited dark vocal folds. • Analyses of 6 other clinical science articles indicated an association between cannabis inhalation and respiratory problems that were reduced with smoking cessation or switching to vaporizing. Lung function was maintained in light cannabis smoke exposure after long-term use	5/11
Mun[29] 2020	*Population:* healthy, pain-free adults (≥18 years)	*Databases searched:* PsycINFO, Cochrane, Google Scholar, Embase, and Pubmed	*Number of citations identified in Search:* 926	• Five of 8 (62.5%) studies demonstrated an analgesic benefit of inhaled cannabis on at least one QST outcome measure. These positive findings should be interpreted against the backdrop of several null results and inconsistencies—both	7/11

United States	*Intervention:* cannabis use (inhaled) *Comparator:* non-users *Outcome:* analgesia through heat stimuli, cold pain response analgesia, electrical stimuli analgesia, dose-response analgesia, analgesia through heat stimuli, mechanical stimuli analgesia, electrical stimuli analgesia, mechanical stimuli analgesia	*Years searched:* inception to August 2018 *Key words used:* cannabis, Cannabinoid, Analgesia, Quantitative sensory testing, Experimental pain testing, Pain, Chronic pain *Inclusion criteria:* Peer-reviewed publications were eligible for full-text review contingent on the following criteria: (1) relevant search terms appeared in the abstract, (2) the publication was written in the English language, (3) the study included human subjects only, (4) at least one cannabinoid agent (i.e, plant-based or synthetic) was used, (5) at least one QST measure was used, (6) the article was accepted for publication before August 2018, and (7) the full text was available; For data extraction: (1) the study included a placebo control, and (2) individuals were randomized to drug conditions *Exclusion criteria:* not reported	*Number of studies included:* 39 *Number of patients in all included studies:* not reported	within and across studies—in the type of QSTresponse affected and the dose at which analgesia was observed. • Hyperalgesia was observed in 2 studies, and in one study, this was observed at a high dose, when lower doses in the same study produced null and analgesic effects. This suggests an inverted U dose–response relation between inhaled cannabis and QST outcomes. Also, most studies were based on experienced cannabis users. • No study examined the analgesic effects of inhaled cannabis on chemical or visceral stimuli. • It is difficult to provide a meaningful conclusion for analgesia through heat stimuli, as only one study was available. The pattern of responses was not consistent across sensory domains tested in the study. No study examined the analgesic effects of combined THC/CBD formulations on a cold, chemical, or visceral stimulus.	
Pizzol[39] 2019 Israel	*Population:* male *Intervention:* cannabis use (smoking) *Comparator:* non-users *Outcome:* prevalence of erectile dysfunction	*Databases searched:* PubMed, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials *Years searched:* inception to January 18, 2019 *Key words used:* (cannabis OR cannabi* OR Marihuana OR Marihuanas OR Marijuana OR Marijuanas OR Ganja OR Hashish OR 9tetrahydrocannabinol* OR delta3-thc OR sp-104 OR sp104 OR 1972-08-3 OR Dronabinol OR Marinol OR dronabinolum OR deltanyne OR tetrahydrocann* OR cannabinoid* OR canabinoid*) AND (ED OR erectile function OR sexual dysfunction OR sexual function) *Inclusion criteria:* (i) observational studies (case–control, cross-sectional and prospective) reporting the prevalence/incidence of ED in people using cannabis versus nonusers; (ii) using a validated tool for the detection of ED (e.g., the International Index of Erectile Function, IIEF-5) and (iii) reporting the use of cannabis, also through self-reported information	*Number of citations identified in Search:* 452 *Number of studies included:* 5 *Number of patients in all included studies:* 3395	• The overall prevalence of ED in cannabis users was 69.1% (95% CI: 38.0–89.1), whilst the correspondent figure in controls was 34.7% (95% CI: 20.3–52.7). • The OR of ED in cannabis users was almost four times that of controls (OR = 3.83; 95% CI: 1.30–11.28; p = .02) even if characterized by high heterogeneity (I2 = 90%) and the prediction intervals overlapped 1.00 (95% CI: 0.35–7.26). Data suggest that ED is twice as high in cannabis users compared to controls.	7/11

		Exclusion criteria: (i) did not include humans and (ii) a control group of cannabis users was not included			
Pradhan[25] 2018 Nepal	*Population:* human patients with myocardial infarction *Intervention:* marijuana use *Comparator:* non-users *Outcome:* in-hospital mortality	*Databases searched:* PubMed, CENTRAL, and EMBASE *Years searched:* July 2001 to July 2018 *Key words used:* marijuana, cannabinoids, tetrahydrocannabinol, myocardial infarction, acute myocardial infarction, ischemic heart disease, coronary artery disease, MI, AMI, IHD, CAD *Inclusion criteria:* studies published in the English language; studies assessing the impact of marijuana use on outcomes following MI *Exclusion criteria:* studies that aimed to assess the impact of marijuana use on the outcomes of other diseases such as cancer, glaucoma, and posttraumatic stress disorder; case reports, editorials, and correspondences	*Number of citations identified in Search:* 27 *Number of studies included:* 4 *Number of patients in all included studies:* 3,729,840	• in-hospital mortality in patients with MI was significantly reduced among marijuana users compared with non-users in retrospective studies but not in cohort studies	4/11
Rajanahally[38] 2019 United States	*Population:* male *Intervention:* marijuana use *Comparator:* not reported *Outcome:* male factor infertility, male sexual health/hormones	*Databases searched:* Medline, Embase *Years searched:* inception to May 2017 *Key words used:* 'marijuana', 'cannabis', 'cannabinoids', 'endocannabinoids', 'infertility' (male), 'semen analysis', 'hypogonadism', 'testosterone', 'gonadotropins', 'libido', 'erectile dysfunction', 'testicular cancer', 'germ cell tumor', 'prostate cancer', 'penile cancer', 'bladder cancer', 'kidney cancer', 'renal carcinoma' *Inclusion criteria:* English studies; vitro models, case series, case–control, cohort designs	*Number of citations identified in Search:* 1897 *Number of studies included:* 30 *Number of patients in all included studies:* not reported	• Overall, cannabis consumption has a negative impact on fertility using semen parameters as a surrogate. • There did not appear to be a significant relationship between long-term cannabis consumption and the HPG axis hormones in the clinical studies. • Marijuana consumption appears to be an independent risk factor for the development of testicular germ cell tumors.	4/11

		Exclusion criteria: not human, in vitro, or mammalian species; review articles			
Ravi[17] 2018 United States	*Population:* participants older than 12 years *Intervention:* any form of marijuana (plant or pharmaceutical) *Comparator:* not reported *Outcome:* dyslipidemia, cardiovascular mortality, stroke, diabetes, acute myocardial infarction, diabetes, all-cause mortality	*Databases searched:* PubMed, MEDLINE, EMBASE, PsycINFO, Cochrane Library *Years searched:* 1 January 1975 to 30 September 2017 *Key words used:* reported in supplement *Inclusion criteria:* observational studies (cohort, case–control, cross-sectional) and interventional studies (randomized controlled trials, experimental studies) that enrolled participants older than 12 years and were published in English; exposure criterion was any form of marijuana (plant or pharmaceutical); main outcomes of interest were cardiovascular risk factors and outcomes *Exclusion criteria:* case reports, case series, review articles, editorials, and in vitro and animal studies	*Number of citations identified in Search:* 1669 *Number of studies included:* 24 *Number of patients in all included studies:* not reported	• Evidence examining the effect of marijuana on diabetes, dyslipidemia, acute myocardial infarction, stroke, or cardiovascular and all-cause mortality was insufficient.	7/11
Reece[23] 2009 Australia	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users, occasional users *Outcome:* cardiovascular, genotoxic, mutagenic, oncogenic effects, respiratory	*Databases searched:* Medline, PubMed, PsychInfo, Google Scholar, Scopus, ProQuest, Web of Knowledge, EbscoHost *Years searched:* not reported *Key words used:* cannabis, marijuana, marihuana, toxicity, complications, mechanisms *Inclusion criteria:* original data; describe mechanisms; published in “recent years” *Exclusion criteria:* not reported	*Number of citations identified in Search:* 5198 *Number of studies included:* not reported *Number of patients in all included studies:* not reported	• Chronic cannabis use associated with worsening psychotic symptoms, violent suicides, higher anxiety, increased inflammation in lungs, and can cause cardiovascular issues • Heavy chronic use may be associated with bone loss and certain cancers	2/11

Sims[28] 2018 Canada	*Population:* boys and girls who are less than 18 years *Intervention:* recreational or medicinal cannabis *Comparator:* not reported *Outcome:* pubertal timing, final weight, final height, pubertal tempo	*Databases searched:* MEDLINE, Embase, Cochrane Database of Systematic Reviews, Central, PsycINFO, CINAHL, Web of Science, and SPORTDiscus *Years searched:* Inception to February 2018 *Key words used:* reported in article *Inclusion criteria:* studies including boys and girls who are less than 18 years of age with exposure to recreational or medicinal cannabis were included in this review. The use of cannabis included smoked, ingested, and all other modes of exposure to cannabis products as reported. A minimum of 10 study participants were required for the study to be considered eligible for inclusion. Eligible study designs included randomized controlled trials, observational studies, prospective and retrospective cohort studies, and case–control studies *Exclusion criteria:* case reports, reviews, and preclinical or animal studies	*Number of citations identified in Search:* 578 *Number of studies included:* 0 *Number of patients in all included studies:* 0	• Zero studies included	5/11
Tetrault[33] 2007 United States	*Population:* general population *Intervention:* acute and chronic cannabis exposure *Comparator:* non-users *Outcome:* airway response, pulmonary function or respiratory complications	*Databases searched:* Medline, PsychInfo, EMBASE *Years searched:* January 1966 until October 2005 *Key words used:* not reported *Inclusion criteria:* not reported *Exclusion criteria:* not humans; did not report results of respiratory complications or pulmonary functioning; case series with fewer than 10 subjects	*Number of citations identified in Search:* 965 *Number of studies included:* 34 *Number of patients in all included studies:* 14,183	• Acute cannabis inhalation associated with bronchodilation, but not present in long-term smokers • Long-term smoking associated with increased respiratory complications such as cough, sputum production, and wheeze	8/11

Vaitla[40] 2020 United States	*Population:* kidney transplant recipients *Intervention:* cannabis use *Comparator:* non-users *Outcome:* all-cause allograft failure, mortality due to transplant, death-censored graft failure	*Databases searched:* Ovid MEDLINE, EMBASE, and The Cochrane Library Databases *Years searched:* inception until September 2019 *Key words used:* cannabis OR "cannabis use" OR "cannabis addiction" OR "cannabis smoking" OR Marijuana) AND ("kidney transplantation" OR "kidney graft" OR "patient history of kidney transplantation"/expOR"patient history of kidneytransplantation"OR"transplantation"OR"transplant"OR"kidney transplant"OR"renal transplant"). *Inclusion criteria:* observational studies and clinical trials providing 95% confidence intervals (CI) data on the prevalence and impact of cannabis use on outcomes after kidney transplantation *Exclusion criteria:* in vitro studies, pediatric patient population, animal studies, case reports, correspondences, or review articles	*Number of citations identified in Search:* 411 *Number of studies included:* 4 *Number of patients in all included studies:* 55897	• The use of cannabis was not significantly associated with all-cause allograft failure (OR = 1.31, 95% CI 0.70-2.46, I2 = 71%) • The use of cannabis was not significantly associated with mortality (OR = 1.52, 95% CI 0.59- 3.92, I2 = 15%). • The use of cannabis was significantly associated with increased death-censored graft failure with pooled ORof 1.72 (95% CI 1.13-2.60).	7/11
Wijarnpreecha[129] 2018 United States	*Population:* chronic hepatitis C virus infected patients *Intervention:* cannabis use *Comparator:* non-users *Outcome:* advanced liver fibrosis risk	*Databases searched:* MEDLINE and EMBASE *Years searched:* inception to December 2017 *Key words used:* cannabis" and "hepatitis C" *Inclusion criteria:* (1) case-control, cross-sectional, or cohort studies that investigated the risk of advanced liver fibrosis among HCV-infected patients who use cannabis compared with those who do not use cannabis and (2) odds ratios (OR), relative risks, hazard ratios, or standardized incidence ratios with 95% confidence	*Number of citations identified in Search:* 784 *Number of studies included:* 3 *Number of patients in all included studies:* 898	• The risk of advanced liver fibrosis among HCV-infected patients who use cannabis was numerically higher than those who do not use cannabis, although the result did not achieve statistical significance (pooled odds ratio, 1.77; 95% confidence interval, 0.78–4.02). The statistical heterogeneity was high with an I2 of 75%.	5/11

		intervals (CI) or sufficient raw data to calculate these ratios were provided. *Exclusion criteria:* case reports, letters to editor, review articles, basic science studies, animal studies, or interventional studies, did not report the outcome of interest, were descriptive studies without comparators			
Mental Health Effects					
Author **Year** **Country**	**PICO**	**Search strategy**	**Studies included**	**Key outcomes**	**Quality Assessment**
Bartoli[68] 2019 Italy	*Population:* adults with bipolar I, II or not otherwise specified disorder in any current episode (euthymic, manic/hypomanic, depressive), with or without mixed features. *Intervention:* current and lifetime cannabis use disorder, defined as a problematic pattern of cannabis use leading to clinically significant impairment or distress *Comparator:* no cannabis mis-use *Outcome:* **s**uicide attempt, defined as a potentially self-injurious behavior, associated with at least some intent to die	*Databases searched:* Medline, Embase, PsychINFO *Years searched:* inception to July 2018 *Key words used:* cannabis, marijuana, bipolar, mania, suicide *Inclusion criteria:* observational studies providing cross-sectional or longitudinal data on the association between cannabis use disorder and suicide attempts in individuals with bipolar disorder *Exclusion criteria:* studies considering suicidal thoughts or ideation, but not suicidal acts, as well as those selecting only children or adolescents; studies with incomplete data, such as conference abstracts and dissertations, and grey literature that did not undergo peer review process	*Number of citations identified in Search:* 169 *Number of studies included:* 13 *Number of patients in all included studies:* 15654	• "The random-effects meta-analysis, based on 6375 subjects from eleven studies, estimated a cross-sectional association between cannabis use disorder and history of suicide attempts (OR=1.35; p=0.01; I2=41.7%). • Meta-regression analyses showed that effect size was not influenced by any study characteristics. Publication bias was not detectable. • We could not perform a meta-analysis exploring the longitudinal association between cannabis use disorder and suicide attempts, due to the lack of suitable data"	7/11
Ben Amar[61] 2007	*Population:* general population	*Databases searched:* PubMed, PsychInfo	*Number of citations identified in Search:* 622	• Cannabis use was associated with psychosis in those with a vulnerability to psychosis • Cannabis use associated with worsening of psychotic symptoms	3/11

Canada	*Intervention:* cannabis use *Comparator:* non-users *Outcome:* psychosis	*Years searched:* January 1962 until June 2005 *Key words used:* cannabis or marijuana, schizophrenia or psychosis *Inclusion criteria:* longitudinal studies, reviews; addresses the causal nature of the cannabis/psychosis relationship *Exclusion criteria:* not reported	*Number of studies included:* 15 *Number of patients in all included studies:* 107,691		
Borges[67] 2016 Mexico	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users *Outcome:* suicide ideation, suicide attempt, death by suicide	*Databases searched:* Medline, PsychInfo, Google Scholar, public-use databases *Years searched:* 1990(1995 for acute use) until February 2015 *Key words used:* cannabis, marijuana, marihuana, suicide, suicide attempt, suicide ideation, suicidal, suicidality *Inclusion criteria:* English language; original articles, critical review reports, public use data on cannabis use and suicidality *Exclusion criteria:* synthetic cannabinoids	*Number of citations identified in Search:* not reported *Number of studies included:* not reported *Number of patients in all included studies:* not reported	• Minimal evidence for acute cannabis use and suicidality • Any and heavy cannabis use associated with suicidality, but heterogeneity and publication bias high • Chronic cannabis use and death by suicide: OR = 2.56 (95% CI = 1.25-5.27) • Any cannabis use and suicidal ideation: OR = 1.43 (95% CI = 1.13-1.83) • Heavy cannabis use and suicidal ideation: OR = 2.53 (95% CI = 1.00-6.39) • Any cannabis use and suicide attempt: OR = 2.23 (95% CI = 1.24-4.00) • Heavy cannabis use and suicide attempt: OR = 3.20 (95% CI = 1.72–5.94)	5/11
Calabria[18] 2010 Australia	*Population:* general population *Intervention:* cannabis exposure	*Databases searched:* Medline, EMBASE, PsychInfo *Years searched:* January 1990 until January 2008	*Number of citations identified in Search:* not reported *Number of*	• Insufficient data to determine all-cause mortality is higher in users compared to the general population • Heavy cannabis use associated with increased risk of poor driving • Cannabis use associated with suicide, but minimal evidence	5/11

	Comparator: not specified *Outcome:* death by suicide	*Key words used:* cannabis, mortality, cohort, drug use *Inclusion criteria:* human studies; mortality associated with cannabis use or dependence *Exclusion criteria:* not focused on cannabis or mortality; review articles and case series	*studies included:* 19 *Number of patients in all included studies:* 387,635 (cannabis use not reported)		
Cancilliere[48] 2018 United States	*Population:* adolescents *Intervention:* cannabis use *Comparator:* control (varied between studies) *Outcome:* anxiety	*Databases searched:* MedLine, PsycINFO, PsycARTICLES, EMBASE, and PubMed databases, Google Scholar *Years searched:* 1992 to 2015 *Key words used:* Marijuana, Anxiety, Adolescent, Brain Imaging *Inclusion criteria:* (1) participants were human participants, (2) it was an original study (no reviews or meta-analyses), (3) measures included evaluation of marijuana use, and (4) measures included evaluation of anxiety (i.e., anxiety disorders and anxiety symptoms) *Exclusion criteria:* not reported	*Number of citations identified in Search:* 477 *Number of studies included:* 27 *Number of patients in all included studies:* 25975	• The majority of studies revealed an association between marijuana use and anxiety, but the strength of the association and the variability among the studies' designs limited the comparison and warrants additional investigation. Only five studies met criteria that used brain imaging techniques, and findings were non-conclusive.	4/11
Colizzi[27] 2018 United Kingdom	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users, occasional users	*Databases searched:* MEDLINE, Web of Science and Scopus *Years searched:* Inception (assumed) to June 2018 *Key words used:* (“marijuana”, “cannabis”, “THC/ delta-9-tetrahydrocannabinol/dronabinol”), its pattern of use (“heavy”, “regular”, “frequent”, “light”, “non-regular”, “occasional”), the study design	*Number of citations identified in Search:* 1252 *Number of studies included:* 36	• Research evidence tends to suggest that the acute effects of single cannabinoid administration are less prominent in regular cannabis users compared to non-regular users. • Studies of repeated cannabinoid administration more consistently suggest less prominent effects upon repeated exposure. Cognitive function is the domain showing the highest degree of tolerance, with some evidence of complete absence of acute effect (full tolerance). The acute intoxicating, psychotomimetic, and cardiac effects are also blunted upon regular exposure, but to a lesser extent (partial tolerance). Limited research also	6/11

	Outcome: psychopathological symptoms	(“acute”, “challenge”, “administration”), and the outcome of interest (“tolerance”, “sensitization”), *Inclusion criteria:* (1) human studies, (2) studies investigating the impact of a single administration of Δ9-THC or cannabis in 2 or more populations with different levels of previous cannabis exposure (i.e. frequent users, occasional users, naïve individuals), (3) studies investigating the impact of a single administration of Δ9-THC or cannabis in a single population with variation in the extent of previous cannabis exposure (i.e. correlating the acute effect of Δ9-THC or cannabis on the outcome measure with the extent of previous cannabis exposure), or (4) studies investigating the impact of repeated administration of Δ9-THC or cannabis in population(s) of cannabis users (i.e. (re)assessing the outcome measure after every administration). *Exclusion criteria:* (1) studies where the effects of Δ9-THC or cannabis were not investigated under experimental conditions, (2) studies in which groups were not differentiated in terms of previous cannabis exposure, (3) studies which primarily assessed the effects of psychoactive substances other than cannabis, and (4) studies which primarily/ exclusively assessed cannabinoid pharmacokinetics without investigating other outcomes of interest	*Number of patients in all included studies:* 1047	suggests development of tolerance to other behavioral, physiological, and neural effects of cannabis.	
Crippa[49] 2009 United Kingdom	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users *Outcome:* anxiety	*Databases searched:* Medline, PsychLIT, EMBASE *Years searched:* inception until August 2008 *Key words used:* cannabis, marijuana, THC, tetrahydrocannabinol, delta-9-tetrahydrocannabinol, cannabinoids, anxiety, panic, phobia, stress *Inclusion criteria:* not reported *Exclusion criteria:* not reported	*Number of citations identified in Search:* not reported *Number of studies included:* not reported *Number of patients in all included studies:* not reported	• Frequent cannabis use associated with higher levels of anxiety compared to non-users • Higher prevalence of anxiety disorders in chronic cannabis users than the general population; anxiety disorders may increase risk of using cannabis • Anxiety associated with cannabis withdrawal • No association between cannabis use and an increased risk in developing anxiety disorders	4/11
Esmaeelzadeh[45]	*Population:* adolescents, young adults	*Databases searched:* Medline, PubMed, Cochrane Library, Embase, and PsycINFO.	*Number of citations*	• Pooled results showed a positive association between depression and use of cannabis (OR = 1.29, 95% CI: 1.10–1.51).	5/11

2018 Canada	*Intervention:* cannabis or CUD *Comparator:* non-users *Outcome:* anxiety, depression	*Years searched:* 2000 to 2017 *Key words used:* depression; anxiety; alcohol; cannabis; tobacco; adolescents; young adults; U.S.; Canada *Inclusion criteria:* (1) English language peer-reviewed articles, available in full text, with human studies, published from 2000 to 2017; (2) depression/anxiety symptoms or disorders (major depressive disorder, panic disorder, social anxiety disorder, specific phobias, generalized anxiety disorder) data measured by using standardized scales, diagnostic criteria, self-reported surveys or diagnosed by healthcare professionals; (3) substance use (alcohol, cannabis, or tobacco) or disorder data presented, analyzed, and discussed; (4) target population that included adolescents and/or young adults; (5) only studies conducted in the US or Canada; and (6) data was either presented as an odds ratio (OR) or permitted the OR to be calculated. *Exclusion criteria:* case series and case report. Newspaper, conference posters, dissertations were excluded; (1) exposures other than those of interest in this study, such as cessation/withdrawal from substances, use of e-cigarettes, opiates, cocaine, methamphetamine, sedative, and hallucinogens; (2) outcomes other than those of interest in this study, such as suicide ideations, bipolar disorder, mania, postpartum depression, and hypomania; (3) the recruited population was other than that of interest in this study, such as adults, participants who were pregnant, specific ethnic groups or gender, military veterans, participants with comorbid chronic medical illnesses such as diabetes, cardiovascular or lung diseases.	*identified in Search:* 2616 *Number of studies included:* 14 *Number of patients in all included studies:* not reported	• Significant associations were also found between anxiety and use of cannabis (OR = 1.36, 95% CI: 1.02–1.81). • A unidirectional relationship was also observed with cannabis use leading to depression (OR = 1.33, CI = 1.19–1.49).	
Farris[62] 2020 Canada	*Population:* clinical high risk for psychosis *Intervention:* cannabis/CUD	*Databases searched:* Medline, CINAHL, EBM reviews, Embase, PsychINFO, Google Scholar *Years searched:* inception to November 2018 *Key words used:* cannabis, Clinical high risk, Psychosis, Systematic review, Meta-analysis	*Number of citations identified in Search:* 1226 *Number of studies included:* 36	• The most commonly reported association with cannabis use was transition to psychosis, although the pooled relative risk (RR) was not statistically significant (RR = 1.11, 95% confidence interval = 0.89–1.37). • For all other outcomes including symptoms, cognition, trauma, and family history, the evidence was limited.	5/11

	Comparator: non-users, no CUD, no recent use *Outcome:* transition to psychosis, psychotic symptoms	*Inclusion criteria:* (1) individuals characterized as CHR or UHR using any criteria, (2) a measurement of cannabis use, regardless of dose, frequency or duration, (3) one or more of the following outcomes: cognitive functioning, symptom presentation, transition to psychosis, history of trauma, family history of psychosis or cannabis use in general, and (4) studies designed as randomized controlled trials (RCTs) and non-randomized observational studies. *Exclusion criteria:* case reports, review articles with no original research reported, editorials and other studies not meeting inclusion criteria were excluded.	*Number of patients in all included studies:* 4055		
Garfield[42] 2013 Australia	*Population:* illicit substance users *Intervention:* substance use *Comparator:* non-users *Outcome:* anhedonia	*Databases searched:* PubMed, PsychInfo, Medline *Years searched:* not reported *Key words used:* anhedonia, drug, substance, alcohol, nicotine, dependence, addiction, abuse *Inclusion criteria:* human samples; lifetime history of a defined substance use disorder or long-term daily use; measured anhedonia *Exclusion criteria:* reviews; non-substance related psychiatric disorders	*Number of citations identified in Search:* 245 *Number of studies included:* 32, 3 on cannabis *Number of patients in all included studies:* not reported	• Those with baseline cannabis abuse reported higher levels of anhedonia than those with no baseline cannabis abuse • Baseline anhedonia did not predict cannabis use • Abstinence from cannabis was associated with a decrease in anhedonia	3/11
Gibbs[44] 2015 United Kingdom	*Population:* people with bipolar disorder I or II *Intervention:* cannabis exposure	*Databases searched:* PsychInfo, Cochrane, Scopus, EMBASE, Medline *Years searched:* 1980 until June 2014	*Number of citations identified in Search:* 781 *Number of studies included:* 6	• Cannabis use increases the likelihood, severity or duration of manic phases in those with bipolar disorder (OR = 2.97, 95% CI = 1.80-4.90) • Cannabis use also associated with increased risk of hypomanic symptoms in those at high risk of developing bipolar disorder	9/11

	Comparator: non-users, those without bipolar *Outcome:* manic symptoms	*Key words used:* cannabis, marijuana, delta-9-tetrahydrocannabinol, cannabinoids, cannabidiol, cannabinol, tetrehydrocannabivarin, bipolar disorder, manic depressive disorder, mania, hypomania, manic depression, dipolar spectrum, onset, trigger, induce*, course *Inclusion criteria:* prospective primary experimental, prospective, cohort, longitudinal designs; participants had bipolar I or II or described as experiencing mania; clinical and subclinical mania symptoms and episodes; English language *Exclusion criteria:* participants primarily diagnosed with a psychotic disorder; non-English	*Number of patients in all included studies:* 2,391		
Gobbi[46] 2019 Canada	*Population:* adolescents to young adults *Intervention:* cannabis use *Comparator:* non-users *Outcome:* depression in Young Adulthood, anxiety in young adulthood, suicide ideations, suicide attempts	*Databases searched:* Medline, Embase, CINAHL, PsycInfo, and Proquest Dissertations and Theses *Years searched:* inception to January 2017 *Key words used:* marijuana and mental illness, including symptoms of mental illness *Inclusion criteria:* reported in an original article ina peer-reviewed journal; included population-based data that were collected longitudinally and prospectively; the exposure variable referred specifically to cannabis; outcome measures referred specifically to depression, suicidal behavior, anxiety (often comorbid to depression), or mixed anxiety-depressive symptoms; the outcome variable was controlled for at baseline; assessed cannabis use in adolescents younger than 18 years (at least 1 assessment point) and then again assessed them for depression in young adulthood (aged 18-32 years); data were either presented as an odds ratio; and controlled and adjusted for the following confounding factors: age, sex, and depression and/or anxiety at baseline. *Exclusion criteria:* not reported	*Number of citations identified in Search:* 3142 *Number of studies included:* 35 *Number of patients in all included studies:* not reported	• The OR of developing depression for cannabis users in young adulthood compared with nonusers was 1.37 (95%CI, 1.16-1.62; I2 = 0%). • The pooled OR for anxiety was not statistically significant: 1.18 (95%CI, 0.84-1.67; I2 = 42%). • The pooled OR for suicidal ideation was 1.50 (95%CI, 1.11-2.03; I2 = 0%), and for suicidal attempt was 3.46 (95%CI,	7/11

Hindley[53] 2020 United Kingdom	*Population:* healthy humans *Intervention:* THC *Comparator:* placebo *Outcome:* total Psychiatric symptoms severity, general psychiatric symptoms, positive symptom severity, negative symptom severity	*Databases searched:* MEDLINE, Embase, and PsycINFO *Years searched:* inception to May 21, 2019 *Key words used:* cannabis, synthetic cannabinoids, psychiatric symptoms *Inclusion criteria:* double blind studies that included healthy participants; reported symptom changes in response to acute administration of intravenous, oral, or inhaled THC or CBD; contained either a placebo condition or concurrent administration of THC plus CBD, or placebo CBD; used a within-person, crossover design; reported total, positive, or negative symptoms using BPRS or PANSS; and presented data allowing the calculation of the standardized mean difference and deviation between the THC and placebo condition *Exclusion criteria:* studies not involving a control condition, using an active control, or administering concurrent medication; studies with absence of measures in either the THC or control condition; studies not written in English; studies not reporting original data; studies only providing p or t values, change measurements, or effect sizes; studies with two or fewer participants in each group; and studies involving concurrent administration of other pharmacological compounds	*Number of citations identified in Search:* 372 *Number of studies included:* 22 *Number of patients in all included studies:* not reported	• 15 eligible studies involving the acute administration of THC and four studies on CBD plus THCadministration were identified. • Compared with placebo, THC significantly increased total symptom severity with a large effect size (assessed in nine studies, with ten independent samples, involving 196 participants: SMC 1·10 [95% CI 0·92–1·28], p<0·0001); positive symptom severity (assessed in 14 studies, with 15 independent samples, involving 324 participants: SMC 0·91 [95% CI 0·68–1·14], p<0·0001); and negative symptom severity with a large effect size (assessed in 12 studies, with 13 independent samples, involving 267 participants: SMC 0·78 [95% CI 0·59–0·97], p<0·0001). • In the systematic review, of the four studies evaluating CBD's effects on THC-induced symptoms, only one identified a significant reduction in symptoms. • Positive symptom severity standardized mean change: 0.91 (95% CI: 0.68 to 1.14) • Negative symptom severity standardized mean change: 0.78 (95% CI: 0.59 to 0.97) • General psychiatric symptoms standardized mean change: 1.01 (95% CI: 0.77 to 1.25)	6/11
Hosseini[43] 2019 Canada	*Population:* Cannabis-using adolescents (aged 12-17 years) and young adults (aged 18-25 years) *Intervention:* cannabis use of any frequency, potency, amount, and duration during adolescence or young adulthood (<25 years) *Comparator:* not reported	*Databases searched:* MEDLINE, EMBASE, PsycINFO *Years searched:* inception to March 2018 *Key words used:* cannabis, marijuana abuse, marijuana, smoking, depression, depressive disorders, anxiety, anxiety disorders, psychosis, psychotic disorders, schizophrenia, age and initiation, and age at onset *Inclusion criteria:* Cohort, cross-sectional, and case-control studies; studies reporting on cannabis-using adolescents (aged 12-17 years) and young adults (aged 18-25 years) or studies	*Number of citations identified in Search:* 320 *Number of studies included:* 23 *Number of patients in all*	• Overall, most studies found that earlier initiation of cannabis use in youth was associated with greater psychotic symptomatology, compared with later initiation or no use. • 6 of the 11 included studies reported findings indicating that earlier use of cannabis was linked to higher symptom levels of depression and anxiety	6/11

	Outcome: psychosis symptoms, depression/ anxiety	that dichotomized age of initiation of cannabis use; cannabis use of any frequency, potency, amount, and duration during adolescence or young adulthood (<25 years); studies reporting on psychosis, depression, or anxiety symptoms or disorders, using any method of diagnosis; any follow-up time; any setting; English-language studies only *Exclusion criteria:* not reported	*included studies:* not reported		
James[64] 2013 United Kingdom	*Population:* adolescents *Intervention:* cannabis use *Comparator:* non-users *Outcome:* schizophrenia onset	*Databases searched:* EMBASE, Medline, PubMed, PsychLIT, LILACS *Years searched:* inception until December 2012 *Key words used:* marijuana, cannabis, delta-9-tetrahydro- cannabinol, THC, cannabidiol, CBD, neuroimaging, brain imaging, computerized tomography, CT, magnetic resonance, MRI, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, diffusion tensor MRI, DTI- MRI, spectroscopy, MRS. *Inclusion criteria:* case-control design; healthy controls; participants under 19 *Exclusion criteria:* non-neuroimaging studies of cannabis use; participants older than 19; subjects with other neurological or psychiatric disorders or other substance abuse disorders	*Number of citations identified in Search:* 141 *Number of studies included:* 24 *Number of patients in all included studies:* 450	• May be associated with adolescent-onset schizophrenia due to loss of grey and white matter, but minimal evidence exists	5/11
Kedzoir[52] 2014 Germany	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users	*Databases searched:* PsychInfo, Medline *Years searched:* inception until March 2013 *Key words used:* cannabis, marijuana, marihuana, affective disorder, anxiety disorder, anxiety, misus*, abus*, depend*, harmful use, harmful usage	*Number of citations identified in Search:* 267 *Number of studies included:* 31	• Those with anxiety are more likely to use cannabis or have cannabis use disorder • Anxiety and cannabis use: OR = 1.24 (95% CI = 1.06-1.45) • Anxiety and cannabis use disorder: OR = 1.68 (95% CI = 1.23-2.31) • Comorbid anxiety and cannabis use disorder may require more treatment than cannabis use disorder alone	9/11

	Outcome: anxiety and cannabis use disorder, anxiety	*Inclusion criteria:* general population; anxiety diagnosis with or without cannabis use; odds ratios; cannabis use with or without anxiety *Exclusion criteria:* no data from healthy non-users; data from people seeking treatment for cannabis use disorder or other psychiatric disorders other than anxiety or depression; inadequate data	*Number of patients in all included studies:* 173,577		
Kraan[63] 2016 Netherlands	*Population:* those at ultra-high risk of psychosis *Intervention:* cannabis use *Comparator:* non-users, general population *Outcome:* psychosis	*Databases searched:* EMBASE, Medline, PsychInfo *Years searched:* 1996 until August 2015 *Key words used:* clinical high risk, attenuated positive symptoms, brief limited intermittent psychotic symptoms, genetic risk and deterioration, basic symptoms, familial high risk, prodrom*, at risk mental state, ultra high risk, attenuated psychotic symptoms, high risk, substance use, substance abuse, substance use disorder, cannabis, marijuana, tobacco, hallucinogens, cannabis misuse, risk factors, psychosis, schizophrenia, schizo*, psychoti* *Inclusion criteria:* individuals meeting ultra-high risk criteria; reported the effect of cannabis use on transition to psychosis; prospective design; English language *Exclusion criteria:* cannabis use not assessed separately	*Number of citations identified in Search:* 5560 *Number of studies included:* 7 *Number of patients in all included studies:* 330	• No relationship between any cannabis use and transition to psychosis in ultra-high risk individuals (OR = 1.14, 95% CI = 0.856-1.524) • Cannabis abuse or dependence was significantly associated with transition to psychosis (OR = 1.75, 95% CI = 1.135-2.710)	10/11
Large[54] 2011 Australia	*Population:* patients with psychotic disorders *Intervention:* cannabis, alcohol, other psychoactive drugs *Comparator:* patients with psychosis but no drug use	*Databases searched:* CINAHL, EMBASE, Medline, PsychInfo, ISI Web of Science *Years searched:* inception until June 2010 *Key words used:* schizophrenia, psychosis, substance, dual diagnosis, drug abuse, cannabis, alcohol, amphetamine, cocaine, age	*Number of citations identified in Search:* 1293 *Number of studies included:* 83	• Significantly earlier age of onset of psychosis in cannabis users compared to non-users (2.70 years earlier, p<0.001) • General substance use also associated with earlier age of onset • Alcohol not associated with earlier onset	9/11

	Outcome: age of onset of psychosis	*Inclusion criteria:* English language; reported the use of a psychoactive drug other than tobacco; compared age of onset with a control group *Exclusion criteria:* not reported	*Number of patients in all included studies:* 8167		
Lev-Ran[47] 2014 Canada	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users *Outcome:* depression	*Databases searched:* EMBASE, Medline, PsychInfo, ISI Web of Science *Years searched:* inception until December 2012 *Key words used:* cannabis, marijuana, marihuana, depression, depressed, depressive disorder, mood, mood disorder, affective disorder, dysthymia *Inclusion criteria:* original paper in a peer-review journal; population-based data collected longitudinally and prospectively; cannabis use; depression was controlled at baseline; odds ratio *Exclusion criteria:* not reported	*Number of citations identified in Search:* 4764 *Number of studies included:* 14 *Number of patients in all included studies:* 76,058	• Cannabis use associated with risk of developing depression compared to non-users • Any cannabis use and depression: OR = 1.17 (96% CI = 1.05-1.30) • Heavy cannabis use and depression compared to no or light use: OR = 1.62 (95% CI = 1.21-2.16)	10/11
Mammen[50] 2018 Canada	*Population:* adults (ie, 18+ years of age) meeting criteria for a mood or anxiety disorder at baseline (without comorbidities related to physical illness, schizophrenia, or psychoses), as determined by either clinician interviews or screening instruments with established cutoff thresholds *Intervention:* cannabis use (isolated cannabis without polysubstance use)	*Databases searched:* Embase, MEDLINE, MEDLINE in Process and Other Non-Indexed Citations, MEDLINE Epub Ahead of Print, PsycInfo *Years searched:* inception to May 2017 *Key words used:* extensive search reported in article *Inclusion criteria:* (1) employed a cohort-based longitudinal design; (2) focused on adults (ie, 18+ years of age) meeting criteria for a mood or anxiety disorder at baseline (without comorbidities related to physical illness, schizophrenia, or psychoses), as determined by either clinician interviews or screening instruments with established cutoff thresholds; (3) assessed symptomatic course (operationalized as using multiple follow-up assessments in analysis) and/or	*Number of citations identified in Search:* 10191 *Number of studies included:* 12 *Number of patients in all included studies:* 11959	• Among individuals living with a baseline PTSD, panic disorder, bipolar disorder, or depressive disorder—recent cannabis use was associated with negative symptomatic outcomes (including course of symptoms) over time. • Specifically, the collective findings suggest that individuals using cannabis (ie, any/greater frequency of use in the last 6 months) experienced greater symptom severity and number of symptoms and less occurrence of symptomatic remission and recovery up to 5 years following baseline assessment relative to the comparison groups (ie, no/lesser frequency of use).	8/11

	Comparator: at least 1 comparison/control group (any) *Outcome:* symptoms in anxiety and mood disorders	symptomatic outcome (operationalized as using only 1 follow-up measure) as the dependent variable; (4) assessed at least baseline cannabis use as the independent variable (isolated cannabis without polysubstance use); and (5) included at least 1 comparison/control group *Exclusion criteria:* not reported			
Marconi[65] 2016 United Kingdom	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users *Outcome:* risk of schizophrenia	*Databases searched:* PubMed, EMBASE, PsychInfo *Years searched:* inception until December 31st 2013 *Key words used:* dose-response, daily use, duration, high frequency, heavy use, psychosis, schizophrenia, schizophreni*, cannab*, cannabis, marijuana, marihuana *Inclusion criteria:* peer-reviewed; any language; cohort, cross-sectional; assessed cannabis with a dose criterion before onset of psychosis; psychosis-related outcomes *Exclusion criteria:* subjects who had a mental illness before cannabis use; subjects at ultra-high risk; studies examining comorbidity; studies examining age of onset of psychosis; neuropsychological measures or schizoid personality traits; cannabis not measured by dose	*Number of citations identified in Search:* 571 *Number of studies included:* 16; 10 for meta-analysis *Number of patients in all included studies:* 66,816	• Heavy cannabis use associated with a significant increase in risk of schizophrenia and other psychotic outcomes compared to non-users (OR = 3.90, 95% CI = 2.84-5.34) • Average cannabis use also significantly associated with schizophrenia and psychotic outcomes (OR = 1.97, 95% CI = 1.68-2.31)	7/11
Minozzi[60] 2010 Italy	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users *Outcome:* psychosis	*Databases searched:* Medline, EMBASE, CINAHL *Years searched:* 2000 until August 2007 *Key words used:* substance-related disorders, cannabis, marihuana, marijuana, psychosis, psychotic disorders, schizophrenia, psychotic* *Inclusion criteria:* systematic reviews that assess cannabis and psychosis	*Number of citations identified in Search:* 41 *Number of studies included:* 5 *Number of patients in all*	• Consistent, significant associations between cannabis use and onset of psychotic symptoms • Quality and methodological concerns limit the results	7/11

		Exclusion criteria: not reported	*included studies:* 265,403		
Moore[58] 2007 United Kingdom	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users *Outcome:* psychotic or affective mental health outcomes	*Databases searched:* Medline, EMBASE, CINAHL, PsychInfo, ISI Wed of Knowledge, ISI Proceedings, ZETOC, BIOSIS, LILACS, MedCarib *Years searched:* inception until September 2006 *Key words used:* psychosis, schizophrenia, affective disorder, depression, cannabis (all with synonyms not reported) *Inclusion criteria:* population-based longitudinal or case-control nested studies; humans *Exclusion criteria:* patients with mental illness or substance-related problems; prison populations; RCTs of medical cannabis	*Number of citations identified in Search:* 4804 *Number of studies included:* 11 *Number of patients in all included studies:* not reported	• Increased incidence of psychosis-related outcomes in those who had ever used cannabis (OR=1.41, 95% CI: 1.20-1.65) • Heavy and earlier use increased risk • More frequent cannabis use increased the incidence of any psychotic outcome (OR = 2.09, 95% CI = 1.54-2.84)	7/11
Myles[130] 2016 Australia	*Population:* patients with first episode psychosis *Intervention:* inhaled cannabis *Comparator:* patients with first episode psychosis who do not use cannabis, patients with chronic psychosis *Outcome:* length of time from cannabis use to psychosis	*Databases searched:* Medline, EMBASE, CINAHL, PsychInfo, ISI Web of Science *Years searched:* October 2014 to "current" *Key words used:* psychosis, schizophrenia, cannabis, marijuana *Inclusion criteria:* English language; cohorts that reported on first episode psychosis; inhaled organic cannabis; could be included in a meta-analysis	*Number of citations identified in Search:* 2113 *Number of studies included:* 61 *Number of patients in all included studies:* 10,762	• 33.7% (95% CI = 29-38%) of subjects used cannabis prior to psychosis • Pooled interval between first cannabis use and age of psychosis onset was 6.3 years (SMD = 1.56, 95% CI = 1.40-1.72) • Cannabis use higher in patients with first episode psychosis compared to patients with chronic, long-term psychosis	6/11

		Exclusion criteria: not first episode; subjects suffering from drug-induced or organic psychoses; subjects recruited for a clinical trial or RCT; synthetic or oral cannabinoids; cohorts that were part of a larger cohort			
Myles[56] 2012 Australia	*Population:* Patients with schizophrenia-spectrum disorder *Intervention:* cannabis or tobacco use *Comparator:* tobacco users compared to cannabis users *Outcome:* age of onset of psychosis	*Databases searched:* EMBASE, Medline, PsychInfo, ISI Web of Science *Years searched:* inception until September 2011 *Key words used:* cannabis, marijuana, tobacco, nicotine, smoking, schizophrenia, psychosis *Inclusion criteria:* separately reported substance and non-using groups; report age of onset of psychosis; be suitable for meta-analysis *Exclusion criteria:* bipolar, psychotic depression, substance-induced psychosis	*Number of citations identified in Search: 589* *Number of studies included:* 38 for cannabis; 40 for tobacco *Number of patients in all included studies:* 3199 for cannabis; 5562 for tobacco	• Tobacco not significantly associated with earlier ago of onset of psychosis • Cannabis significantly associated with earlier age of onset of schizophrenia spectrum psychosis and broad psychosis • Age of psychosis was 32 months earlier (SMD = 0.399, 95% CI = -0.493- -0.306) for cannabis users compared to non-users	10/11
Ragazzi[131] 2018 Brazil	*Population:* non-clinical populations *Intervention:* cannabis use *Comparator:* not reported *Outcome:* psychotic-like experiences	*Databases searched:* PubMed/Medline, Web of Science, PsycInfo *Years searched:* inception to September 2017 *Key words used:* (“Community Assessment of Psychic Experiences” OR CAPE) AND (psychosis OR psychotic) AND (cannabis OR marijuana OR hashish OR hash OR skunk) *Inclusion criteria:* observational studies (cohort, case-control and cross sectional), investigated cannabis as a potential risk factor for PLEs, evaluated non-clinical samples, used the CAPE to assess PLEs and were published in English, Spanish or Portuguese	*Number of citations identified in Search:* 51 *Number of studies included:* 19 *Number of patients in all included studies:* not reported	• cannabis use may be associated with PLEs in population-based samples; the results indicate that the higher the use of cannabis, the higher the probability of developing PLEs, particularly among young individuals. Although the results were more consistent in the positive dimension, cannabis use was also associated with the negative and depressive dimensions of the Community Assessment of Psychic Experiences scale	5/11

		Exclusion criteria: studies with only clinical samples, case reports, editorials and reviews; experimental studies; studies that did not present detailed description of the methodology and statistical analysis, such as conferences abstracts			
Reece[23] 2009 Australia	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users, occasional users *Outcome:* severity of symptoms	*Databases searched:* Medline, PubMed, PsychInfo, Google Scholar, Scopus, ProQuest, Web of Knowledge, EbscoHost *Years searched:* not reported *Key words used:* cannabis, marijuana, marihuana, toxicity, complications, mechanisms *Inclusion criteria:* original data; describe mechanisms; published in "recent years" *Exclusion criteria:* not reported	*Number of citations identified in Search:* 5198 *Number of studies included:* not reported *Number of patients in all included studies:* not reported	• Chronic cannabis use associated with worsening psychotic symptoms, violent suicides, higher anxiety, increased inflammation in lungs, and can cause cardiovascular issues • Heavy chronic use may be associated with bone loss and certain cancers	2/11
Rey[41] 2004 Australia	*Population:* children and adolescents *Intervention:* cannabis use *Comparator:* non-users *Outcome:* behavioural problems, juvenile psychiatric disorder	*Databases searched:* Medline, Pre-Medline, PsychInfo, EMBASE, Web of Science *Years searched:* 1994 until 2004 *Key words used:* not reported *Inclusion criteria:* not reported *Exclusion criteria:* not English; adults	*Number of citations identified in Search:* Not reported *Number of studies included:* Not reported *Number of patients in all included studies:* Not reported	• Cannabis has a low non-continuation rate • About 10% of users have cannabis dependence; more common in those who start use young • Data on cannabis as a gateway drug is inconclusive • Symptoms of anxiety and depression higher in females, but results are inconclusive	1/11
Semple[57]	*Population:* general population	*Databases searched:* EMBASE, PsychInfo, Medline	*Number of citations identified in*	• Early use of cannabis was associated with an increased risk of psychosis (OR = 2.9, 95% CI = 2.4-3.6)	5/11

2005 United Kingdom	*Intervention:* cannabis use *Comparator:* non-users *Outcome:* age of onset of psychosis	*Years searched:* 1966 until January 2004 *Key words used:* cannabis, schizophrenia, other key words not reported *Inclusion criteria:* original data; case-control studies; exposure to cannabis preceded schizophrenia or schizophrenia-like psychosis *Exclusion criteria:* not reported	*Search:* not reported *Number of studies included:* 11, 7 in meta-analysis *Number of patients in all included studies:* 113,802	• Dose-related effect seen in individuals who used cannabis during adolescence, those who previously experience psychosis, and those at genetic high risk	
Szoke[66] 2014 France	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users *Outcome:* psychometric schizotypy	*Databases searched:* PubMed, PsychInfo *Years searched:* inception until 2013 *Key words used:* schizot*, psychotic-like, psychosis-proneness, cannabi*, THC, marijuana *Inclusion criteria:* humans; English-language *Exclusion criteria:* not reported	*Number of citations identified in Search:* 63 *Number of studies included:* 29 *Number of patients in all included studies:* 21,736	• Life-time cannabis use and current cannabis use were both associated with higher schizotypy scores	3/11
Twomey[51] 2017 United Kingdom	*Population:* general populations *Intervention:* cannabis use *Comparator:* non-users	*Databases searched:* PsycINFO, MEDLINE, EMBASE, CINAHL Plus, Social Science Citation Index and System for Information on Grey Literature in Europe (SIGLE) *Years searched:* inception to 20 May 2016	*Number of citations identified in Search:* 609 *Number of studies included:* 10	• cannabis use was associated with anxiety, with a very small OR of 1.15 (95% CI 1.03 to 1.29) and minimal heterogeneity (I2=23%). Restricting the analysis to high-quality studies (k=5) decreased the OR to a nonsignificant level of 1.04 (95% CI 0.91 to 1.19; I2=0%), as did adjusting for publication bias displayed in the funnel plot (OR=1.08; 95% CI 0.94 to 1.23).	7/11

	Outcome: Anxiety (operationalized as a binary variable, using diagnosis (Diagnostic and Statistical Manual of Mental Disorders (DSM)/International Statistical Classification of Diseases and Related Health Problems (ICD)) or cut-off points on standardized scales measuring symptoms)	*Key words used:* (ie, "cannabis" or "marijuana") were combined with keywords relating to anxiety (ie,"anxiety" or "anxiety disorder") and study design ("cohort" or "longitudinal" or "follow-up" or "long term" or "panel" or "historical" or "developmental") *Inclusion criteria:* Prospective longitudinal studies with general population samples. Exposure: Cannabis use (or use frequency), operationalized as a binary variable, measured at baseline. Outcome: Anxiety, operationalized as a binary variable, using diagnosis (Diagnostic and Statistical Manual of Mental Disorders (DSM)/International Statistical Classification of Diseases and Related Health Problems (ICD)) or cut-off points on standardized scales measuring symptoms. Manuscript: No limit was set according to language or peer reviewed status. *Exclusion criteria:* Clinical sample populations; studies only investigating a specific anxiety disorder (eg, panic disorder)	*Number of patients in all included studies:* 58538		
Van der Meer[132] 2012 Netherlands	*Population:* those at clinical high risk for psychosis *Intervention:* cannabis use *Comparator:* non-users *Outcome:* first episode psychosis	*Databases searched:* Medline, PsychInfo, PubMed, EMBASE *Years searched:* 1995 until October 31st 2011 *Key words used:* at risk population*, high risk, UHR, risk factor*, prodromal, prodrome, at * risk, early * symptom*, clinical* * risk, high risk population, psychosis, psychoses, psychotic, psychotic disorder*, prepsychosis, prepsychotic, schizophrenia, schizophrenic, paranoi*, delusion*, hallucination*, hallucinogen*, psychedelic?, psychodelic?, cannabis, cannabinoid*, tetrahydrocannabinol, THC, hashish, marijuana, marijuana, marijuana usage, marijuana smoking, hallucinogenic drugs, psychoactive drug, psychedelic agent* *Inclusion criteria:* English language; contained data on the relation between cannabis use and clinical high risk status or symptomatology; first episode *Exclusion criteria:* papers where cannabis was only analyzed as a confounder or was not analyzed separately	*Number of citations identified in Search:* 729 *Number of studies included:* 11 *Number of patients in all included studies:* 742	• Inconclusive results about cannabis use and severity of symptoms at baseline, pre-psychotic symptoms, and early onset of psychosis • Weak evidence suggesting cannabis may worsen symptoms in younger users	4/11

Van der Steur[59] 2020 Netherlands	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users *Outcome:* risk of psychosis	*Databases searched:* MEDLINE and Embase *Years searched:* 2009 until July 23rd, 2019 *Key words used:* (((((("Cannabis"[Mesh]) OR ((Cannabis[Title/Abstract] OR Marihuana*[Title/Abstract] OR Marijuana*[Title/Abstract] OR Hashish*[Title/Abstract] OR Hemp[Title/Abstract])))) AND (("Psychotic Disorders"[Mesh]) OR ((psychotic disorder*[Title/Abstract] OR psychosis[Title/Abstract] OR psychoses[Title/Abstract] OR psychotic[Title/Abstract])))))) NOT (animals[MeSH Terms] NOT humans[MeSH Terms]). *Inclusion criteria:* Only published, peer-reviewed, and observational studies investigating the relationship between cannabis use and psychosis were considered and were considered and were selected when they examined one of the following moderating factors: 1) patterns of cannabis use (e.g., dose and frequency); 2) age of initiation of cannabis use; 3) type of cannabis used; 4) the individual genetic profile; 5) cannabis use related to the age of onset of psychosis; and 6) the influence of cannabis use on the transition to psychosis in individuals at CHR *Exclusion criteria:* studies that exclusively reported measures of lifetime cannabis use (ever vs. never), that only examined other potential risk factors for psychosis (e.g., childhood trauma), or that reported data from overlapping cohorts	*Number of citations identified in Search:* *Number of studies included:* *Number of patients in all included studies:*	• Frequent cannabis use and the consumption of high-potency cannabis increase the risk of psychosis • Furthermore, cannabis use lowers the age of onset of psychosis by 3 years, and increases the risk of transition in subjects at clinical high risk for psychosis.	3/11
Zammit[133] 2008 United Kingdom	*Population:* patients with psychosis *Intervention:* cannabis use *Comparator:* patients with psychosis without cannabis use	*Databases searched:* Medline, EMBASE, CINAHL, PsychInfo, ISI Web of Knowledge, ISI Proceedings, ZETOC, BIOSIS, LILACS, MedCarib *Years searched:* inception until November 2006 *Key words used:* psychosis, schizophrenia, hallucinations, delusions, substance abuse, and unspecified synonyms	*Number of citations identified in Search:* 15,303 *Number of studies included:* 13	• Cannabis use was associated with increased relapse and rehospitalization and decreased treatment adherence • Inconsistent results about cannabis use and severity of symptoms	9/11

	Outcome: severity of symptoms, other adverse outcomes	*Inclusion criteria:* longitudinal studies of people with psychosis; case-control nested studies *Exclusion criteria:* comorbid psychosis and cannabis misuse or dependence	*Number of patients in all included studies:* not specified		
Neurocognitive Effects					
Author **Year** **Country**	**PICO**	**Search strategy**	**Studies included**	**Key outcomes**	**Quality Assessment**
Blithikioti[82] 2019 Spain	*Population:* human *Intervention:* cannabis use (abstinence of less than 5 days) *Comparator:* non-users (abstinence of 5 days or more) *Outcome:* memory, psychomotor function, attention, behavioral tasks, executive function	*Databases searched:* PubMed, Science Direct, Scopus *Years searched:* inception to March 2018 *Key words used:* cannabis, marihuana, marijuana, delta 9-tetrahydrocannabinol, hashish, cerebellum *Inclusion criteria:* (1) neuroimaging and behavioral studies that included the cerebellum on the neuroimaging analysis or measured cerebellar-dependent functions, (2) studies that described the cannabis use pattern of participants (acute or chronic; and for chronic users, duration and/or pattern of consumption), (3) studies that reported the pre-study abstinence period (this criterion was applied to all studies except for structural neuroimaging studies where this criterion is not relevant), and (4) studies that included a comparison group of healthy controls (placebo-controlled trials with a within-subject design for acute effects were also included); (5) English-only *Exclusion criteria:* (1) animal studies, (2) studies with participants with psychiatric or neurological comorbidities or substance use disorders other than cannabis and/or nicotine, and (3) studies that used synthetic cannabinoids or medicinal marijuana.	*Number of citations identified in Search:* 348 *Number of studies included:* 40 *Number of patients in all included studies:* not reported	• The most consistent findings include (1) increases in cerebellar gray matter volume after chronic cannabis use, (2) alteration of cerebellar resting state activity after acute or chronic use, and (3) deficits in memory, decision making, and associative learning. Age of onset and higher exposure to cannabis use were frequently associated with increased cannabis induced alterations • Chronic cannabis use is associated with alterations in cerebellar structure and function, as well as with deficits in behavioral paradigms that involve the cerebellum (eg, eyeblink conditioning, memory, and decision making).	5/11

Bogaty[90] 2018 Australia	*Population:* diagnosed with psychotic disorder *Intervention:* cannabis use *Comparator:* non-users *Outcome:* IQ, sustained attention, cognitive flexibility, conceptual set-shifting, working memory (verbal), processing speed, verbal learning, verbal memory, motor inhibition, verbal fluency, non-spatial memory	*Databases searched:* PubMed, Medline, PsychInfo *Years searched:* inception to October 2016 *Key words used:* psychosis (i.e. schizophrenia, schizophreniform, psychosis, schizoaffective, schizo*, FEP, first, episode), cannabis (i.e. cannabis, marijuana, THC, tetrahydrocannabinol), and cognition (i.e. neuropsycho*, neurocognit*, cogniti*), *Inclusion criteria:* (1) diagnosis of a psychotic disorder according to DSM (i.e. Schizophrenia Spectrum and Other Psychotic Disorders) or ICD (i.e. Schizophrenia Spectrum and Other Primary Psychotic Disorders) criteria; (2) studies had to compare a psychotic (or schizophrenia spectrum disorder) cannabis-using group to an appropriate clinical control group (i.e. psychotic nonusers); (3) cannabis was the predominate substance used by patients, as stated by the authors in the methodology; (4) the assessment of traditional neuropsychological functions using valid and reliable tests, used routinely in clinical practice (Strauss et al., 2006); and (5) sufficient statistical data were reported for transformation into effect sizes (ES), or the relevant data were available from the original researchers; English-only; human only *Exclusion criteria:* (1) were diagnosed with a substance/medication-induced psychotic disorder, or were intoxicated at time of testing; or (2) investigated individual components of cannabis (e.g. tetrahydrocannabinol [THC] or cannabidiol [CBD] on their own); or (3) investigated synthetic cannabis. Only studies with the largest sample were included in the instance of overlapping samples.	*Number of citations identified in Search:* 308 *Number of studies included:* 14 *Number of patients in all included studies:* 1430	• CANN+ performed worse on several cognitive domains (i.e. premorbid IQ, current IQ, verbal learning, verbal working memory, motor inhibition) compared to CANN-. • The association between age and performance in CANN+ cognition was varied, with older age predictive of worse performance in processing speed, sustained attention, verbal memory, and better performance in verbal learning and very fluency. CANN+ outperformed CANN- in tests of conceptual set-shifting.	4/11
Borgan[98] 2019 United Kingdom	*Population:* human *Intervention:* cannabis use	*Databases searched:* EMBASE, MEDLINE, PsycINFO, and PsycARTICLES databases *Years searched:* 1950 to Sep 2018	*Number of citations identified in Search:* 2494 *Number of*	• delta-9 tetrahydrocannabinol (THC) (1.5–5 mg/kg) relative to placebo impaired performance on non-spatial memory tests, whereas only high THC doses (67 mg/kg) impaired spatial memory.	4/11

	Comparator: unclear *Outcome:* spatial memory, non-spatial memory	*Key words used:* cannabinoid 1 receptor, CB1R agonists, CB1R antagonists, Cognition, Memory *Inclusion criteria:* (1) original research articles; (2) in vivo experimental methods; (3) comparison of drug relative to control (either placebo or vehicle); and (4) use of a memory paradigm (see supplementary materials 1 for full descriptions of memory paradigms). *Exclusion criteria:* (1) review articles; (2) in vitro experimental methods; (3) failure to use a memory paradigm; (4) use of receptor knockout paradigms; (5) use of disease models; and (6) use of concurrent environmental manipulations (e.g. stress or food deprivation models).	*studies included:* 38 *Number of patients in all included studies:* not reported		
Broyd[134] 2016 Australia	*Population:* general population *Intervention:* cannabis exposures *Comparator:* non-users *Outcome:* cognitive outcomes	*Databases searched:* PubMed, Scopus *Years searched:* January 2004 until February 2015 *Key words used:* cannabi*, marijuana, cognit*, memory, attention*, learning, inhibit*, impuls*, reward, decision making, executive function*, information process*, performance, functional brain imaging, fMRI, event related potential, electroencephalogram, not rats or mice or review or MDMA or ecstasy or amphetamine *Inclusion criteria:* neuropsychological or cognitive experimental tasks; regular or former cannabis users or following acute administration of cannabis; human participants *Exclusion criteria:* cannabis is not the primary drug; trait measures of cognition; major psychopathology or neurological conditions; animals; neuroimaging, electrophysiological, or autonomic measures as the primary outcome; treatment; "real world" tasks; case studies	*Number of citations identified in Search:* 6441 *Number of studies included:* 105 *Number of patients in all included studies:* not reported	• Impaired verbal learning and memory and psychomotor functioning in chronic and occasional users • Inconsistent evidence regarding working memory, attention, and executive functioning, but some evidence suggests impairment • Many impairments exist after abstinence	4/11
Colizzi[27] 2018	*Population:* humans	*Databases searched:* MEDLINE, Web of Science and Scopus	*Number of citations identified in Search:* 1252	• Research evidence tends to suggest that the acute effects of single cannabinoid administration are less prominent in regular cannabis users compared to non-regular users. • Studies of repeated cannabinoid administration more consistently suggest less prominent effects	6/11

United Kingdom	*Intervention:* cannabis use *Comparator:* non-users, occasional users *Outcome:* cognitive function	*Years searched:* Inception (assumed) to June 2018 *Key words used:* ("marijuana", "cannabis", "THC/ delta-9-tetrahydrocannabinol/dronabinol"), its pattern of use ("heavy", "regular", "frequent", "light", "non-regular", "occasional"), the study design ("acute", "challenge", "administration"), and the outcome of interest ("tolerance", "sensitization"), *Inclusion criteria:* (1) human studies, (2) studies investigating the impact of a single administration of Δ9-THC or cannabis in 2 or more populations with different levels of previous cannabis exposure (i.e. frequent users, occasional users, naïve individuals), (3) studies investigating the impact of a single administration of Δ9-THC or cannabis in a single population with variation in the extent of previous cannabis exposure (i.e. correlating the acute effect of Δ9-THC or cannabis on the outcome measure with the extent of previous cannabis exposure), or (4) studies investigating the impact of repeated administration of Δ9-THC or cannabis in population(s) of cannabis users (i.e. (re)assessing the outcome measure after every administration). *Exclusion criteria:* (1) studies where the effects of Δ9-THC or cannabis were not investigated under experimental conditions, (2) studies in which groups were not differentiated in terms of previous cannabis exposure, (3) studies which primarily assessed the effects of psychoactive substances other than cannabis, and (4) studies which primarily/ exclusively assessed cannabinoid pharmacokinetics without investigating other outcomes of interest	*Number of studies included:* 36 *Number of patients in all included studies:* 1047	upon repeated exposure. Cognitive function is the domain showing the highest degree of tolerance, with some evidence of complete absence of acute effect (full tolerance). The acute intoxicating, psychotomimetic, and cardiac effects are also blunted upon regular exposure, but to a lesser extent (partial tolerance). Limited research also suggests development of tolerance to other behavioral, physiological, and neural effects of cannabis.	
Farris[62] 2020 Canada	*Population:* clinical high risk for psychosis *Intervention:* cannabis/CUD *Comparator:* non-users, no CUD, no recent use	*Databases searched:* Medline, CINAHL, EBM reviews, Embase, PsychINFO, Google Scholar *Years searched:* inception to November 2018 *Key words used:* cannabis, Clinical high risk, Psychosis, Systematic review, Meta-analysis *Inclusion criteria:* (1) individuals characterized as CHR or UHR using any criteria, (2) a measurement of cannabis use, regardless of dose, frequency or duration, (3) one or more of the	*Number of citations identified in Search:* 1226 *Number of studies included:* 36 *Number of patients in all*	• The most commonly reported association with cannabis use was transition to psychosis, although the pooled relative risk (RR) was not statistically significant (RR = 1.11, 95% confidence interval = 0.89–1.37). • For all other outcomes including symptoms, cognition, trauma, and family history, the evidence was limited. •	5/11

	Outcome: cognition	following outcomes: cognitive functioning, symptom presentation, transition to psychosis, history of trauma, family history of psychosis or cannabis use in general, and (4) studies designed as randomized controlled trials (RCTs) and non-randomized observational studies. *Exclusion criteria:* case reports, review articles with no original research reported, editorials and other studies not meeting inclusion criteria were excluded.	*included studies:* 4055		
Figueiredo[92] 2020 Portugal	*Population:* adults *Intervention:* chronic/ heavy cannabis use *Comparator:* non-users, minimal use *Outcome:* motor impulsivity, attention, cognitive impulsivity, cognitive flexibility, emotional cognition, short term memory, long term memory, motor impulsivity	*Databases searched:* PubMed, Embase, MEDLINE, SciELO, Baidu Scholar, CNKI *Years searched:* January 2010 to January 2019 *Key words used:* cannabis, Chronic Cannabis use, Neuropsychology, Impulsivity, Memory, Intelligence, Attention, Cognitive flexibility, Meta-analysis *Inclusion criteria:* had to describe human participants with an age of 18 years or older, experiencing chronic cannabis use and/or a cannabis dependency diagnosed operationally by Diagnostic and Statistical Manual of Mental Disorders criteria; they reported at least one standardized neurocognitive test, with name and/or description of the task; Case control, longitudinal, and/or cross sectional studies; cannabis was the primary drug of interest and the manuscripts were published in English, Spanish, Portuguese and Chinese. *Exclusion criteria:* (a) Cohorts including participants under 18 years of age. (b) Cohorts including participants with a current illicit polydrug use and dependence. (c) Cohorts including participants with a diagnosis of psychiatric or neurological illnesses. (d) Cohorts including participants with alcohol dependence. (e) Cohorts including participants with any history of serious head injury. (f) Studies focusing on structural or functional neuroimaging parameters as a primary outcome. (g) Studies in which cannabis users were not asked to abstain prior to testing.	*Number of citations identified in Search:* 2827 *Number of studies included:* 13 *Number of patients in all included studies:* 1382	• There was a low cross-sectional association between neurocognitive impairments and chronic cannabis use in cognitive impulsivity, cognitive flexibility, attention, short-term memory and long-term memory. • No association was found between chronic cannabis use and motor impulsivity. By analysing a specific target population with strict inclusion criteria, these findings provide inconclusive evidence that there are cognitive impairments associated with chronic cannabis use.	7/11

Ganzer[135] 2016 Germany	*Population:* general population *Intervention:* cannabis use *Comparator:* current users, non-users *Outcome:* neurocognitive functioning	*Databases searched:* EMBASE, Ovid MEDLINER, PsychInfo, PSYNDEXplus Literature *Years searched:* 2004 until 2015 *Key words used:* cannabi*, THC, marijuana, marihuana, neuro*, cognit*, assess*, abilit*, affect*, process*, function*, impair*, residual, long-term, abstinen*, abstain*, lasting, non-acute, non-intox*, persist* *Inclusion criteria:* clinical trials; humans *Exclusion criteria:* subjects with a history of chronic medical and neurological illness or severe psychiatric disorder, or substance use disorder; animal studies; case reports, expertises, commentaries, books	*Number of citations identified in Search:* 1038 *Number of studies included:* 38 *Number of patients in all included studies:* 2025	• Poorer attention, motor function, and memory and learning in abstinent users than non-users • Impairments in inhibition, impulsivity, and decision making in abstinent users, but inconsistent evidence • Highly inconsistent evidence with regards to visual spatial functioning • Differences in activation patterns and structural differences in the brain of abstinent users compared to controls	9/11
Gonzalez[136] 2002 United States	*Population:* general population *Intervention:* cannabis use *Comparator:* non-users, current users *Outcome:* neurocognitive effects	*Databases searched:* not reported *Years searched:* not reported *Key words used:* not reported *Inclusion criteria:* non-acute neuropsychological effects of cannabis; humans; adults; English language *Exclusion criteria:* not reported	*Number of citations identified in Search:* 1014 *Number of studies included:* 40 *Number of patients in all included studies:* 741	• Poorer motor performance, executive function, reaction time, learning, and verbal domains • However, results highly inconsistent and generally poor quality	5/11
Gorey[137]	*Population:* general population	*Databases searched:* Medline, Cochrane Library, and PsycInfo	*Number of citations*	• First, in humans, general executive functioning seems to be more impaired in adolescent, frequent cannabis users compared to adult, frequent	3/11

2019 Netherlands	*Intervention*: age and cannabis use *Comparator:* other ages and cannabis non-use *Outcome:* cannabis intoxication and cognition, cannabis use history and cognition	*Years searched:* inception up to July 19, 2018 *Key words used:* cannabis, cognition, adolescence/adulthood, and study type *Inclusion criteria:* human samples must have included both adolescents younger than 18 and adults older than 18; must have explored cannabis exposure as the independent variable and cognitive outcomes as the dependent variable; analyses msut have included an age by cannabis exposure interaction on cognition, with age being explored either categorically (adolescent or adult) or continuously; must have administered measures during adolescence or adulthood, not retrospectively; must have used primary quantitative data collection methods (eg: no case studies, review papers); must have solely looked at cannabis-related factors as the independent variables (eg: did not explore cannabis-related factors in individuals with psychosis); must be written in English; must be published in a peer-reviewed journal before July 19, 2018 *Exclusion criteria:* studies that assessed cannabis exposure retrospectively	*identified in Search:* 1482 *Number of studies included:* 21 *Number of patients in all included studies:* not reported	cannabis users. Second, in humans, age-effects may be most prominent among very heavy and dependent users, which may suggest CUD-specific effects. Third, in humans, craving and inhibitory control may not decrease as much after cannabis intoxication in adolescents compared to adults.	
Grant[97] 2003 United States	*Population:* adults *Intervention:* cannabis use *Comparator:* non-users, occasional users *Outcome:* neurocognitive performance learning and forgetting	*Databases searched:* Medline/HealthSTAR, PsychInfo, BioSys, Current Contents, Dissertation Abstracts international, Article First, Science Citation Index Expanded, Social Science Citation Index *Years searched:* not reported *Key words used:* marijuana, marijuana, tetra-hydrocannabinol, THC, cannabis, neuro*, cognitive, assessment, ability, effects, processes, impairment, cognition, drug effects *Inclusion criteria:* includes a cannabis only group and control group; can calculate effect size; measures neuropsychological tests; reports length of abstinence *Exclusion criteria:* not humans or adults	*Number of citations identified in Search:* 1014 *Number of studies included:* 11 for meta-analysis *Number of patients in all included studies:* 1032; 632 users	• Inconsistent results on all measures except learning and forgetting, both of which were small • Learning: -0.21 (99% CI = -0.39- -0.022 • Forgetting: -0.27 (99% CI = -0.49- -0.044)	4/11

Lovell[91] 2020 Tasmania	*Population:* human adults, free from major neuropsychological or physical comorbidities, including mental diagnoses (other than cannabis use disorder in the cannabis group) *Intervention:* regular and long-term cannabis use (mean ≥2 years and mean ≥4 days per week of cannabis use) *Comparator:* non- or minimal substance-using control group, either with or without an additional comparison group *Outcome:* learning and memory, attention, global cognition, cognitive abilities, executive functioning, decision making, working memory, information processing	*Databases searched:* PubMed, PsycINFO, CINAHL, Scopus *Years searched:* inception to May 22, 2019 *Key words used:* (cannabis or marijuana or tetrahydrocannabinol) AND (chronic or residual or persistent or nonacute or long-term or abstinen* or abstain* or lasting) AND (cognition or cognitive processes or cognitive impairment or executive function or neuroc* or neurop*) *Inclusion criteria:* (a) human adults; (b) free from major neuropsychological or physical comorbidities, including mental diagnoses (other than cannabis use disorder in the cannabis group); (c) participants reporting regular and long-term cannabis use (mean ≥2 years and mean ≥4 days per week of cannabis use); (d) sufficient information to determine effect size; (e) non- or minimal substance-using control group, either with or without an additional comparison group; and (f) studies written in English. *Exclusion criteria:* (a) case studies; (b) qualitative research; (c) participants under 18-years-old; and (d) not reporting length of cannabis abstinence	*Number of citations identified in Search:* 1019 *Number of studies included:* 30 *Number of patients in all included studies:* 1613	• Long-term, regular, recreational cannabis use is associated with small deficits in learning and memory (g=-0.33, p<.001, 95% CI [-0.46, -0.19]) • There were nonsignificant differences and small effect sizes for attention (g=0.05, p=.703, 95% CI [-0.21, 0.31]), information processing (g=-0.11, p=.349, 95% CI [-0.34, 0.12]), and working memory (g=0.01, p=.933, 95% CI [-0.23, 0.25]) • Long-term, regular, recreational cannabis use is associated with small deficits in global cognition (g=-0.25, p<.001, 95% CI [-0.35,-0.15]) • Cannabis use duration, age of onset, and prolonged abstinence (≥25 days) did not influence outcomes, except group differences in executive function were nonsignificant in analyses of prolonged abstinence. • Long-term, regular, recreational cannabis use is associated with small deficits in executive functioning (g=-0.18, p<.008, 95% CI [-0.31, -0.05]) • Moderate and significant effect for decision-making, with worse performance in the cannabis group (g=-0.52, p=.013, 95% CI [-0.93, -0.11])	8/11
Martin-Santos[77] 2010 United Kingdom	*Population:* adults *Intervention:* cannabis use *Comparator:* non-users *Outcome:* cognitive function	*Databases searched:* EMBASE, Medline, PubMed, LILACS, PsychLIT, books on substance abuse neuroimaging *Years searched:* inception until January 2009 *Key words used:* marijuana, cannabis, delta-9-tetrahydrocannabinol, THC, cannabidiol, CBD, neuroimaging, brain imaging, computerized tomography, CT, magnetic resonance, MRI, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, diffusion tensor MRI, DTI-MRI, spectroscopy, MRS	*Number of citations identified in Search:* 66 *Number of studies included:* 41 *Number of patients in all included studies:* 665	• Lower resting global, prefrontal, and anterior cingulate cortex blood flow in cannabis users, related to impairments in time estimation, attention, working memory, cognitive flexibility, decision making and psychomotor speed • Impaired cognitive efficiency in cannabis users compared to controls	5/11

		Inclusion criteria: for case-control studies: inclusion of a control group of healthy volunteers matched for age, sex, and handedness; users were abstinent for 12 hours before brain scanning; *for experimental administration of cannabinoids:* parallel or cross-over design; participants were abstinent for at least 1 week *Exclusion criteria:* non-neuroimaging studies of cannabis use; neuroimaging studies involving those under 18 years of age; subjects who had other neurological or psychiatric disorders or who tested positive for drugs other than cannabis			
Nader[80] 2018 Brazil	*Population:* humans ≥18 years old *Intervention:* regular cannabis use *Comparator:* not reported *Outcome:* cognition	*Databases searched:* PubMed, LILACS, SciELO *Years searched:* January 2010 to August 2016 *Key words used:* "cannabis" OR "marijuana" AND "cognitive effects" OR "brain imaging" *Inclusion criteria:* (i) original studies that investigated the effects of regular cannabis use on cognition, brain structure and function employing neuropsychological tests and the following neuroimaging techniques: magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET); (ii) studies that compared a group of cannabis users whose principal drug of abuse was cannabis used on a regular basis (as defined by each study protocol) with a group of controls; and (iii) studies with adults (≥18 years); English, Spanish, or Portuguese *Exclusion criteria:* (i) animal studies; (ii) studies among adolescents (< 18 years); (iii) samples with specific neurological or psychiatric disorders; (iv) studies among subjects with any substance use disorder other than cannabis; (v) studies that evaluated medical use of cannabis or cannabinoids; (vi) studies that addressed acute effects only; (vii) studies that focused on neurochemical, genetic or other aspects of cannabis use; and (viii) review articles	*Number of citations identified in Search:* 713 *Number of studies included:* 56 *Number of patients in all included studies:* not reported	• The neuropsychological studies provide evidence for subtle cognitive deficits at least 7 days after heavy cannabis use. The structural neuroimaging studies show growing evidence of abnormalities in hippocampus volume and gray matter density of cannabis users relative to controls; however, morphological changes in other brain regions are more controversial. The functional neuroimaging studies suggest an altered pattern of brain activity associated with cannabis use.	4/11
Platt[99]	*Population:* general population	*Databases searched:* MEDLINE, EMBASE, PsycINFO	*Number of citations*	• cannabis group performed worse than controls on event-based PM tasks (SMD=-0.49, 95% CI: -0.90, -0.08) and time-based PM tasks (SMD=-0.70, 95% CI: -0.80, -0.61)	5/11

2019 United Kingdom	*Intervention:* cannabis use *Comparator:* non-use or light and/or infrequent use of the drug (cannabis) *Outcome:* performance on prospective memory tasks	*Years searched:* inception to March 2017 *Key words used:* 'alcohol', 'cannabis', 'tobacco', 'amphetamine', 'cocaine', 'opioid', 'prospective memory', 'binge drink?' *Inclusion criteria:* (1) were published in an English language peer-reviewed journal, (2) the primary aim was to examine the effects of psychoactive drug-use on PM performance, (3) used a parallel group design with a control condition (consisting of non-using or light and/or infrequent users) and experimental condition (participants who frequently and/or excessively used the primary drug), (4) evaluated PM using a behavioural rather than self-report measure and (5) used a behavioural task that tapped the full complement of cognitive activities required for PM *Exclusion criteria:* studies using tasks that did not incorporate four sequential stages in the execution of an intended future action: (1) formation and encoding of an intention and action plan as well as an evaluation of potential factors that could optimise or impede performance; (2) retention interval where other cognitive activities can potentially interfere with the rehearsal of the encoded intention; (3) self-initiated retrieval of the intention, where a target cue triggers the effortful and controlled search for the intention in memory; (4) actual retrieval and execution of the intention occurs. Studies must have used valid objective measures of PM to incorporate the constituent cognitive processes or activities of these four stages (e.g., a a delay between the encoding and execution of the intention with the delay filled with a secondary ongoing task; cues or prompts to initiate intention retrieval without external reminders)	*identified in Search:* *Number of studies included:* *Number of patients in all included studies:*		
Rabin[138] 2011 Canada	*Population:* patients with schizophrenia *Intervention:* cannabis use *Comparator:* non-users	*Databases searched:* PsychInfo, Medline, PubMed *Years searched:* not reported *Key words used:* schizophrenia, psychosis, cannabis, tetrahydrocannabinol, THC, marijuana, neuropsych*, neurocog*, cognitive impairment	*Number of citations identified in Search:* not reported *Number of studies included:* 8	• Higher neurocognitive functioning in cannabis users compared to non-users	4/11

	Outcome: neurocognition	*Inclusion criteria:* English language; humans; compare schizophrenia cannabis-users to a control group; could be used for meta-analysis; participants have no other concurrent drug or alcohol use disorders *Exclusion criteria:* not reported	*Number of patients in all included studies:* 942; 356 cannabis users		
Ruiz-Veguilla[88] 2012 Spain	*Population:* patients with schizophrenia and first-episode psychosis *Intervention:* cannabis use *Comparator:* non-users *Outcome:* neurological soft signs focused on sensory integration, motor coordination, motor sequencing, and primitive reflexes (ex. audio-visual integration, finger-nose test, gaze)	*Databases searched:* BIOSIS Citation Index SM, BIOSIS Previews, the Cochrane Library, EMBASE, Inspec, ISI Proceedings, Journal Citation Reports, Medline, PsychInfo, PubMed, Web of Science *Years searched:* inception until November 2011 *Key words used:* psycho, schizophreni*, first episode, neurolog* soft signs, neurolog* soft signs, movement* disorder*, NSS, sensory integrati*, motor coordinati*, motor sequenc*, primitive reflex*, audio-visual integrat*, stereognos*, graphaestes*, extinction, right-left confusion, tandem walk*, rapid alternat* movement*, finger-thumb opposition, finger-nose test, rhythm tapping, fist-ring test, rhythm tapping, fist-ring test, fist-edge-palm test, Oszeretski test, gaz*, palmo-mental, snout, grasp*, cannab*, tetrahydrocannab*, THC, marihuana, marijuana, endocannabinoid*, CBD *Inclusion criteria:* Subjects met the clinical definition of psychosis or schizophrenia; any cannabis use; any age and gender; studies were not excluded due to any medications or comorbidities of subjects; all the studies were included irrespective of other design quality issues, and case report studies were also initially considered *Exclusion criteria:* not reported	*Number of citations identified in Search:* 1225 *Number of studies included:* 5, 2 for meta-analysis *Number of patients in all included studies:* 172	• Smoking cannabis was associated with fewer neurological soft signs in psychotic patients than non-users	8/11
Sanchez-Gutierrez[94] 2020 Spain	*Population:* patients with a diagnosis of first-episode psychosis according to the Diagnostic and Statistical Manual of Mental Disorders (patients with psychotic symptoms	*Databases searched:* PubMed, ScienceDirect, Web of Knowledge,Wiley Cochrane Library, PsycInfo (EBSCOHost), and SpringerLink	*Number of citations identified in Search:* 3051	• no significant differences between cannabis-users and non-users with first-episode psychosis with respect to neurocognitive functioning	5/11

	who could have received antipsychotic treatment for less than 12 weeks) *Intervention:* cannabis abuse or dependence *Comparator:* non-users *Outcome:* neurocognitive functioning	*Years searched:* 2008 - July 2018 *Key words used:* "first episode psychosis AND neurocognition AND cannabis," "FEP AND cognition AND cannabis," "Cannabis AND neurocog* AND neuropsycholog* AND FEP," "psychosis AND cognition AND cannabis," "FEP AND IQ AND cannabis," "psychosis & IQ & cannabis," and "FEP AND cognit* AND cannabis." *Inclusion criteria:* cross-sectional and longitudinal studies were included in the systematic review when they met the following criteria: (1) diagnosis of FEP according to the Diagnostic and Statistical Manual of Mental Disorders (patients with psychotic symptoms who could have received antipsychotic treatment for less than 12 weeks); (2) comparison between CU with FEP and NU with FEP; (3) cannabis abuse or dependence with no other comorbid substance use disorder (except for the common mixture of tobacco and cannabis in the same cigarette when patients did not report independent tobacco use); (4) assessment of neuropsychological functioning based on valid and reliable tests commonly used in clinical practice; and (5) sufficient statistical data for transformation into effect sizes from the original researchers *Exclusion criteria:* (1) diagnosis of a category other than FEP within the psychosis spectrum (e.g., schizophrenia, substance-induced psychotic disorders, schizoaffective disorders); (2) studies on the effects of individual components of cannabis on cognitive functioning; (3) studies in which participants had poly-substance use disorders, even if there was a preferential use toward cannabis, given that other substances of abuse (e.g., alcohol, cocaine, and stimulants) are associated with altered cognitive performance [42,43]; (4) studies whose main neuropsychological outcomes required MRI-based assessment; (5) available data on cannabis use classified according to more than two different levels of use (e.g., NU plus 2 or more cannabis use pathways).	*Number of studies included:* 7 *Number of patients in all included studies:* 673		
Schreiner[95]	*Population:* general population	*Databases searched:* PsychInfo, PsycARTICLES, PubMed, Medline	*Number of citations identified in*	• Cannabis use was associated with significant effects on global neurocognition	5/11

2012 United States	*Intervention:* cannabis use *Comparator:* non- or minimal-users *Outcome:* neurocognitive performance	*Years searched:* not reported *Key words used:* marijuana, marihuana, tetra-hydrocannabinol, THC, cannabis, neuro*, cognit*, assess*, ability*, effect*, process*, impair*, residual, long-term, abstinen*, abstain*, lasting, non-acute, persist* *Inclusion criteria:* human subjects; cannabis only users; control group of nonusers or with very limited drug experience; could be included in meta-analysis; behavioral measure of neuropsychological functioning; participants not under the influence of any substances during testing; history of other substance use or psychiatric illness addressed; the period of abstinence from cannabis before testing is reported *Exclusion criteria:* reviews; acute effects only; brain imaging; not humans or chronic users	*Search:* not reported (~800) *Number of studies included:* 33 *Number of patients in all included studies:* 1010 current or former users	• No significant residual effects seen on abstinent users compared to non-users	
Scott[89] 2018 USA	*Population:* human adolescents and/or young adults (with a mean age of 26 years or younger) *Intervention:* heavy, frequent, and/or problematic cannabis use *Comparator:* minimal cannabis user *Outcome:* attention, overall neurocognitive effect, executive functioning: Abstraction/shifting, inhibition, updating/working memory, speed of	*Databases searched:* PubMed, PsycInfo, Academic Search Premier, Scopus *Years searched:* inception to May 12 2017 *Key words used:* reported in supplementary *Inclusion criteria:* only observational, cross-sectional studies were included. (1) assessed human adolescents and/or young adults (with a mean age of 26 years or younger, to include potentially sensitive neurodevelopmental periods); (2) identified heavy, frequent, and/or problematic cannabis use as the primary variable of interest; (3) did not solely identify cannabis as a comorbidity to another substance use or mental health disorder; (4) did not focus on acute effects; (5) included an appropriate comparison group; (6) reported at least 1 standardized	*Number of citations identified in Search:* 1324 *Number of studies included:* 69 *Number of patients in all included studies:* 8727	• Although there is evidence of modest negative effects on cognition in this population, larger controlled trials using validated outcome measures are greatly needed to better understand the role of cannabinoids in cognitive aging, as small sample sizes and variability in study designs limit our ability to draw definitive conclusions at this time. • Effect sizes were significant in the domains of attention (d = −0.21; 95% CI, −0.31 to −0.12; P < .001). • Results indicated a small overall effect size (presented as mean d) for reduced cognitive functioning associated with frequent or heavy cannabis use (d, −0.25; 95%CI, −0.32 to −0.17; P < .001). The magnitude of effect sizes did not vary by sample age or age at cannabis use onset. However, studies requiring an abstinence period longer than 72 hours (15 studies; n = 928) had an overall effect size (d, −0.08; 95%CI, −0.22 to 0.07) that was not significantly	4/11

	processing, learning, delayed memory, motor, verbal/language, visuospatial	neurocognitive test; (7) was written in English; and (8) provided sufficient data to calculate effect sizes *Exclusion criteria:* not reported		different from 0 and smaller than studies with less stringent abstinence criteria (54 studies; n=7799; d, −0.30; 95%CI,−0.37 to −0.22; P = .01). • Effect sizes were significant in the domains of executive functioning-abstraction/shifting(d = −0.30;95%CI,−0.40 to−0.20; P < .001) • Effect sizes were significant in the domains of executive functioning-inhibition (d = −0.25; 95%CI, −0.38 to −0.13; P < .001), • Effect sizes were significant in the domains of executive functioning-updating/working memory (d = −.22; 95%CI, −0.31 to −0.12; P < .001) • Effect sizes were significant in the domains of speed of information processing (d = −0.26; 95%CI,−0.38 to −0.15; P < .001), • Effect sizes were significant in the domains of learning (d = −0.33; 95%CI, −0.42 to −0.24; P < .001), • Effect sizes were significant in the domains of delayed memory (d = −0.26; 95%CI,−0.35 to −0.16; P < .001), • Non significant effect sizes were found in the domains of motor functioning (d = −0.02; 95% CI, −0.22 to 0.18;P = .83). • Non significant effect sizes were found in the domains of verbal/language (d = −0.14; 95%CI,−0.27 to0.001; P = .05), • Non significant effect sizes were found in the domains of visuospatial (d = −0.04;95%CI, −0.16to0.08;P = .53)	
Scott[93] 2019 Switzerland	*Population:* dementia - older adults aged 50+ with and without neurocognitive disorders, Parkinson's disease - older adults aged 50+ with and without neurocognitive disorders, Multiple sclerosis - older adults aged 50+ with and without neurocognitive disorders, HIV - older adults aged 50+ with and without neurocognitive disorders, Pain - older adults aged 50+ with and without neurocognitive disorders	*Databases searched:* PubMed, Scopus, PsycINFO, and Cochrane Library databases *Years searched:* inception to June 3, 2019 *Key words used:* reported in supplementary	*Number of citations identified in Search:* 1641 *Number of studies included:* 26	• Although here is evidence of modest negative effects on cognition in this population, larger controlled trials using validated outcome measures are greatly needed to better understand the role of cannabinoids in cognitive aging, as small sample sizes and variability in study designs limit our ability to draw definitive conclusions at this time.	7/11

	Intervention: cannabis use *Comparator:* non-users *Outcome:* cognitive outcomes	*Inclusion criteria:* focus our review on recent studies published in 2014 or later, Must include human subjects or biological samples obtained from humans, Must either (a) include subjects with a majority or mean age of 50+ or (b) include separate analysis of an older subsample or of aging effects, Must study either phytocannabinoids (e.g., herbal cannabis), synthetic cannabinoids (including those used medically for any indication), or endocannabinoids (e.g., anandamide), Quantitative assessment of cognitive functions that relate to functional capacity or impairment (i.e., not beliefs or biases toward cannabis use) using either performance-based test (e.g., neuropsychological or cognitive screening test) or rating scale/questionnaire that assesses cognition separately from other domains (e.g., psychiatric or motor functioning), Original empirical research (not a review, case study/series, or qualitative study), Available in English *Exclusion criteria:* not reported	*Number of patients in all included studies:* not reported		
Strickland[96] 2020 United States	*Population:* human *Intervention:* cannabis use *Comparator:* not reported *Outcome:* delay discounting	*Databases searched:* PubMed and ProQuest Central *Years searched:* inception to 14 November 2019 *Key words used:* discounting AND (cannabis OR marijuana) *Inclusion criteria:* (a) study included a bivariate association between delay discounting (money or cannabis delay discounting) and cannabis use variables, (b) human participants research, and (c) peer-reviewed publication in an English language journal, Studies were also included if they reported outcomes taken at non contemporaneous time points (e.g., naturalistic longitudinal studies) as long as there were no experimental manipulations that occurred between assessments *Exclusion criteria:* delayed loss discounting	*Number of citations identified in Search:* 1125 *Number of studies included:* 27 *Number of patients in all included studies:* 24782	• A significant, but small, omnibus effect was observed (r =.082, p<0.001) in which greater cannabis use frequency or severity was associated with greater discounting. Incentive structure and outcome type were each significant moderators in a multiple moderator model such that incentivized tasks correlated with severity measures showed stronger associations (r=.234) than hypothetical tasks correlated with quantity-frequency measures (r=.029).	4/11
Prenatal Exposure					

Author, Year of Publication, Country	PICO	Search strategy	Studies included	Key outcomes	Quality Assessment
Carlier[100] 2020 Italy	*Population:* pregnant women *Intervention:* cannabis use during pregnancy *Comparator:* non-users *Outcome:* adverse obstetrical outcomes, fetal neurobehavioral effects	*Databases searched:* PubMed, Scopus, and Web of Science *Years searched:* 1998 to April 2019 *Key words used:* cannabis, cannabinoid, THC, synthetic cannabinoid, pregnancy, in utero, fetal, breastfeeding, neonatal, meconium, umbilical, amniotic, milk, and hair *Inclusion criteria:* not reported *Exclusion criteria:* not English	*Number of citations identified in Search:* not reported *Number of studies included:* not reported *Number of patients in all included studies:* not reported	• Cannabis use during pregnancy is associated with increased risks of adverse obstetrical outcomes, although neurobehavioral effects are still unclear. Analyses of cannabinoids in meconium are well documented, but further research on other unconventional matrices is needed. Adverse effects due to perinatal synthetic cannabinoid exposure are still unknown, and analytical data are scarce.	3/11
Connor[101] 2016 United States	*Population:* pregnant women *Intervention:* cannabis use during pregnancy *Comparator:* non-users *Outcome:* level II or greater nursery admission, low Apga score, low birth weight, small for gestational age, preterm delivery, gestational age at delivery, still birth, spontaneous abortion, perinatal death, placental abruption	*Databases searched:* PubMed/MEDLINE, EMBASE, Scopus, Cochrane Library, ClinicalTrials.gov, and Cumulative Index to Nursing and Allied Health. *Years searched:* inception to August 2015 *Key words used:* "neonatal outcomes," "pregnancy complications", and "marijuana use." *Inclusion criteria:* observational studies including cohort and case–control studies that compared rates of our primary or secondary outcomes in women who used marijuana during pregnancy with women who did not use marijuana during pregnancy	*Number of citations identified in Search:* 2693 *Number of studies included:* 31 *Number of patients in all included studies:* 132718	• Based on pooled unadjusted data, marijuana use during pregnancy was associated with an increased risk of low birth weight (15.4% compared with 10.4%, pooled relative risk [RR] 1.43, 95% confidence interval [CI] 1.27–1.62) and preterm delivery (15.3% compared with 9.6%, pooled RR 1.32, 95% CI 1.14–1.54). However, pooled data adjusted for tobacco use and other confounding factors showed no statistically significant increased risk for low birth weight (pooled RR 1.16, 95% CI 0.98–1.37) or preterm delivery (pooled RR 1.08, 95% CI 0.82–1.43).	8/11

		Exclusion criteria: studies that included marijuana users in the control group or studies that did not investigate any of our prespecified outcomes; studies for which we were unable to extract outcome data for marijuana users separately from other substance users (ie, cocaine users); studies for which we could not extract raw data based on what was presented; case series, case reports, abstracts, unpublished data, expert opinions, review articles, animal studies, and non-English publications.			
Gunn[104] 2016 United States	*Population:* children of women who used cannabis during pregnancy, and women who used cannabis during pregnancy *Intervention:* cannabis use during pregnancy *Comparator:* No cannabis use during pregnancy *Outcome:* birthweight, preterm birth, gestational age at delivery, head circumference, maternal outcomes, maternal anemia, neonatal length, neonatal placement in neonatal ICU	*Databases searched:* PubMed, Medline, EMBASE, CINAHL, PsychInfo, Web of Science and Sociological Abstracts *Years searched:* inception to April 2014 *Key words used:* cannabis, and maternal, fetal, perinatal, and neonatal outcomes; details not reported *Inclusion criteria:* randomized controlled trials, case-control, cross sectional, and cohort studies, investigate effects of prenatal use of cannabis on maternal, fetal, perinatal and neonatal outcomes *Exclusion criteria:* inclusion of women using other illicit drugs in addition to cannabis	*Number of citations identified in Search:* 6854 *Number of studies included:* 24 *Number of patients in all included studies:* not reported	• Women who use cannabis during pregnancy have increased odds of anemia (OR = 1.36. 95% CI = 1.10-1.69) • Infants whose mothers used cannabis during pregnancy had decreased birthweight (OR = 1.77, 95% CI = 1.04-3.01) • Infants whose mothers used cannabis during pregnancy were more likely to be placed in the ICU (OR = 2.02, 95% CI = 1.27-3.21)	8/11
Sharapova[102] 2018 United States	*Population:* children aged 1-6, children aged >6 - 11 *Intervention:* prenatal marijuana exposure *Comparator:* no prenatal marijuana exposure	*Databases searched:* Medline, Embase, PsychInfo, CINAHL EbscoHost, Cochrane Library, Global Health, and ERIC *Years searched:* inception to Aug 2018 *Key words used:* terms for marijuana (e.g., cannabis, hash, ganja), pregnancy (e.g., pregnancy, pregnant women, in-utero), and outcomes (e.g., cognitive disorders, intelligence, learning, executive functions, attention)	*Number of citations identified in Search:* 1943 *Number of studies included:* 21 *Number of patients in all*	• The significant negative associations were mostly drawn from testing of children over 6 years old, and the majority of studies without statistically significant results still showed decrease in neuropsychological functions. These results suggest some potential adverse effects of prenatal marijuana exposure on attention and perceptive abilities, in addition to decreased general cognitive function, memory, impulse control, IQ, and reading comprehension especially in children aged >6 years.	7/11

	Outcome: attention, perceptive abilities, attention, general cognitive function, memory, impulse control, IQ, reading comprehension	*Inclusion criteria:* published or unpublished studies documenting neuropsychological outcomes in children aged 1–11 years who had been prenatally exposed to marijuana. Studies of prenatal exposure to multiple drugs were included if results for marijuana exposure and its associations with the outcomes were reported separately from results for other substance exposures. *Exclusion criteria:* not reported	*included studies:* not reported		
Torres[105] 2020 United States	*Population:* humans, aged 0 to 22 years *Intervention:* prenatal cannabis exposure *Comparator:* no prenatal cannabis exposure *Outcome:* cognitive impairment	*Databases searched:* PsycINFO, PubMed *Years searched:* inception up to December 2017 *Key words used:* cognitive, pregnancy, and marijuana *Inclusion criteria:* (1) full-text publication in peer reviewed journal, (2) available in English, (3) assessed cognitive consequences of prenatal cannabis exposure in humans, and (4) provided quantitative measurement of cognitive performance. *Exclusion criteria:* relied exclusively on questionnaires or brain imaging data as proxies for cognitive functioning.	*Number of citations identified in Search:* 1604 *Number of studies included:* 45 *Number of patients in all included studies:* not reported	• Prenatal cannabis exposure was associated with few effects, negative or positive. Of the 1,004 cognitive outcomes assessed, children with prenatal cannabis exposure performed more poorly on 34 (3.4%) and better on 9 (0.9%) when compared to a control group.	4/11

Williams[103] 2007 Scotland	*Population:* children ages 0-18 followed from birth *Intervention:* maternal exposure to pregnancy *Comparator:* no maternal exposure to toxins during pregnancy *Outcome:* childhood mental health disorders	*Databases searched:* EMBASE, Medline, PsychInfo, SSCI *Years searched:* Inception until 2005 *Key words used:* key words related to longitudinal studies, risk period, measurements, risks, children, substances, and childhood mental health; details not reported *Inclusion criteria:* birth cohort, prospective, longitudinal, twin or prospective epidemiological studies; examine prenatal, prostnatal and/or early childhood risk factors and association with childhood mental health disorders; children 0-18 years old followed from birth *Exclusion criteria:* risk factors not identified as being associated with the prenatal period; the following mental disorders: organic disorder, schizophrenia, manic episode bipolar disorder, sexual dysfunction, and disorders of adult personality and behavior	*Number of citations identified in Search:* 2,968 *Number of studies included:* 100 (6 on cannabis use) *Number of patients in all included studies:* not reported	• Cannabis use during pregnancy impacted child's ability to maintain attention • Children exposed to cannabis were found to have increased depressive symptoms from ages 10-12	4/11

Appendix 4: AMSTAR Quality Assessment

Table 7. AMSTAR Quality Assessment[13] for all Included Reviews

Author	1. Was an a priori design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive search performed?	4. Was the status of publication (e.g., grey lit) used as an inclusion?	5. Was a list of studies (incl. and excl.) provided?	6. Were the characteristics of the included studies provided?	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality of the included studies used appropriately in formulating conclusion?	9. Were the methods used to combine the findings of studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Was the conflict of interest included?	Overall Score
Arnone[84]	can't answer	no	yes	no	no	yes	no	no	NA	NA	no	2
Bartoli[68]	yes	yes	yes	yes	no	yes	no	no	yes	yes	no	7
Batalla[78]	can't answer	yes	yes	yes	no	yes	no	no	NA	NA	yes	5
Batalla[79]	yes	yes	yes	yes	no	yes	no	no	NA	NA	yes	6
Ben[61]	can't answer	can't answer	yes	yes	no	yes	no	no	NA	NA	no	3
Blithikioti[82]	no	yes	yes	yes	no	yes	no	no	yes	no	no	5
Bogaty[90]	can't answer	no	no	no	yes	yes	no	no	yes	yes	no	4
Borgan[98]	no	can't answer	yes	can't answer	no	yes	no	no	yes	yes	no	4
Borges[67]	can't answer	can't answer	yes	yes	no	yes	no	no	yes	yes	no	5
Broyd[134]	can't answer	can't answer	yes	yes	no	yes	no	no	NA	NA	yes	4
Calabria[18]	can't answer	can't answer	yes	yes	no	yes	yes	yes	NA	NA	no	5
Cancilliere[48]	no	yes	yes	yes	no	yes	no	no	can't answer	no	no	4
Carlier[100]	no	can't answer	yes	yes	no	yes	no	no	can't answer	no	no	3
Chisini[16]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	no	9

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Colizzi[27]	can't answer	can't answer	yes	yes	no	yes	yes	yes	yes	no	no	6
Colizzi[126]	yes	can’t answer	yes	yes	no	yes	yes	yes	NA	NA	yes	7
Conner[101]	yes	yes	yes	no	no	yes	yes	yes	yes	yes	no	8
Cookey[83]	can’t answer	yes	yes	yes	no	yes	no	no	NA	NA	yes	5
Crippa[49]	yes	can’t answer	no	yes	no	yes	no	no	NA	NA	yes	4
de Carvalho[72]	yes	yes	yes	yes	no	yes	yes	yes	yes	no	yes	9
Esmaeelzadeh[45]	no	can't answer	yes	yes	no	yes	no	no	yes	yes	no	5
Farooqui[36]	can't answer	yes	yes	yes	no	yes	yes	yes	yes	yes	no	8
Farris[62]	yes	can't answer	yes	yes	no	yes	no	no	yes	no	no	5
Figueiredo[92]	can't answer	can't answer	yes	yes	no	yes	yes	yes	yes	yes	no	7
French[35]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	no	9
Ganzer[135]	can’t answer	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	9
Garfield[42]	can’t answer	can’t answer	no	yes	no	yes	no	no	NA	NA	yes	3
Gates[128]	can’t answer	yes	no	no	no	yes	yes	yes	NA	NA	no	4
Ghasemiesfe[71]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	10
Ghasemiesfe[32]	yes	yes	yes	yes	no	yes	yes	yes	yes	can't answer	no	8

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Gibbs[44]	yes	yes	yes	yes	no	yes	yes	yes	yes	no	yes	9
Gobbi[46]	no	yes	yes	yes	yes	yes	yes	no	yes	can't answer	no	7
Goldenberg[31]	no	can't answer	yes	no	no	yes	no	no	NA	no	no	2
Gonzalez[136]	can’t answer	yes	no	can’t answer	yes	yes	yes	yes	NA	NA	no	5
Gorey[137]	no	no	yes	yes	no	no	no	yes	NA	no	no	3
Grant[97]	can’t answer	yes	no	yes	no	yes	no	no	yes	no	no	4
Grotenhermen[19]	can’t answer	no	yes	yes	no	yes	no	no	NA	NA	yes	4
Gunn[104]	yes	yes	yes	no	no	yes	yes	yes	yes	no	yes	8
Gurney[73]	can’t answer	yes	yes	yes	no	yes	yes	yes	yes	no	yes	8
Hackam[26]	yes	can’t answer	yes	yes	no	yes	no	no	NA	NA	yes	5
Hindley[53]	yes	can't answer	yes	no	no	yes	yes	no	yes	yes	no	6
Hosseini[43]	no	yes	yes	no	yes	yes	yes	no	yes	no	no	6
Huang[70]	yes	can’t answer	yes	yes	no	yes	no	no	NA	NA	yes	5
James[64]	can’t answer	yes	yes	yes	no	yes	yes	no	NA	NA	no	5
Jouanjus[22]	no	no	yes	no	no	yes	no	no	yes	no	no	3
Kedzior[52]	yes	can’t answer	yes	yes	no	yes	yes	yes	yes	yes	yes	9

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Kennedy[34]	no	no	no	no	no	yes	no	no	yes	no	no	2
Korantzopoulos[24]	can't answer	can't answer	yes	yes	no	yes	no	no	NA	NA	yes	4
Kraan[63]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	10
Large[54]	yes	yes	yes	yes	no	no	yes	yes	yes	yes	yes	9
Lev-Ran[47]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	10
Lorenzetti[87]	no	yes	yes	no	no	yes	no	no	yes	yes	no	5
Lovell[91]	yes	yes	yes	no	no	yes	yes	yes	yes	yes	no	8
Malchow[85]	can't answer	yes	no	yes	no	yes	no	no	NA	NA	yes	4
Mammen[50]	yes	yes	yes	yes	no	yes	yes	yes	yes	no	no	8
Marconi[65]	can't answer	yes	yes	yes	no	yes	no	no	yes	yes	yes	7
Martinasek[37]	no	no	yes	yes	no	yes	no	no	yes	no	no	4
Martin-Santos[77]	can't answer	yes	yes	yes	no	yes	no	no	NA	NA	yes	5
Meehan-Atrash[30]	no	yes	yes	no	no	yes	yes	no	yes	no	no	5
Mehra[69]	yes	yes	yes	yes	no	yes	yes	yes	NA	NA	yes	8
Minozzi[60]	can't answer	yes	yes	yes	no	yes	yes	yes	NA	NA	yes	7
Moore[58]	can't answer	yes	yes	yes	no	can't answer	yes	yes	NA	yes	yes	7

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Mun[29]	yes	yes	yes	yes	no	yes	yes	yes	no	no	no	7
Myles[56]	yes	yes	no	yes	no	no	no	no	yes	yes	yes	6
Myles[130]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	10
Nader[80]	no	yes	yes	no	no	yes	no	no	yes	no	no	4
Pizzol[39]	no	yes	yes	yes	no	yes	yes	no	yes	yes	no	7
Platt[99]	no	can't answer	yes	no	no	yes	yes	yes	yes	no	no	5
Pradhan[25]	no	yes	yes	no	no	yes	no	no	yes	no	no	4
Rabin[138]	can’t answer	can’t answer	no	yes	no	yes	no	no	yes	no	yes	4
Ragazzi[131]	no	yes	yes	no	no	yes	yes	no	yes	no	no	5
Rajanahally[38]	no	yes	yes	no	no	yes	no	no	yes	no	no	4
Rapp[81]	can’t answer	yes	yes	yes	no	yes	yes	yes	NA	NA	yes	7
Ravi[17]	yes	yes	yes	no	no	yes	yes	yes	yes	no	no	7
Reece[23]	can’t answer	no	no	yes	no	no	no	no	NA	NA	yes	2
Rey[41]	can’t answer	can’t answer	no	no	no	no	no	no	NA	NA	yes	1
Rocchetti[86]	yes	yes	yes	yes	no	yes	no	no	yes	yes	yes	8
Ruiz-Veguilla[88]	can’t answer	can’t answer	yes	yes	no	yes	yes	yes	yes	yes	yes	8

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Sami[127]	can't answer	can't answer	yes	yes	no	yes	yes	yes	NA	NA	yes	6
Sanchez-Gutierrez[94]	no	yes	yes	no	no	yes	no	NA	yes	yes	no	5
Schreiner[95]	yes	can't answer	no	yes	no	yes	no	no	yes	no	yes	5
Scott[93]	yes	yes	yes	no	no	yes	yes	yes	yes	no	no	7
Scott[89]	no	yes	yes	no	no	yes	no	NA	yes	yes	no	4
Semple[57]	can't answer	can't answer	yes	yes	no	yes	no	no	yes	yes	no	5
Sharapova[102]	no	yes	yes	yes	no	yes	yes	yes	yes	no	no	7
Sims[28]	yes	yes	yes	yes	NA	NA	NA	NA	yes	NA	no	5
Sneider[76]	can't answer	can't answer	no	can't answer	no	yes	no	no	NA	NA	no	1
Song[74]	no	yes	yes	no	no	yes	no	NA	yes	no	no	4
Strickland[96]	no	no	yes	no	no	yes	no	NA	yes	yes	no	4
Szoke[66]	can't answer	can't answer	no	yes	no	yes	no	no	yes	can't answer	no	3
Tetrault[33]	yes	yes	yes	yes	no	yes	yes	yes	NA	NA	yes	8
Torres[105]	no	no	yes	yes	no	yes	no	NA	yes	no	no	4
Twomey[51]	no	no	yes	yes	no	yes	yes	yes	yes	yes	no	7

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Vaitla[40]	no	yes	yes	no	no	yes	yes	yes	yes	yes	no	7
Van der Meer[132]	can't answer	can't answer	yes	yes	no	yes	no	no	NA	NA	yes	4
Van der Steur[59]	no	no	yes	no	no	yes	no	no	yes	no	no	3
Wijarnpreecha[129]	no	yes	yes	no	no	yes	yes	no	yes	no	no	5
Williams[103]	yes	yes	no	yes	no	yes	no	no	yes	NA	yes	6
Zammit[133]	yes	yes	yes	yes	yes	yes	yes	yes	NA	NA	yes	9