Compendium of Medical Cannabis Policy in the United States and Literature Review of Prenatal Cannabis Use and its Association with Adverse Neonatal Outcomes

by

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Abstract

Cannabis, also known as marijuana, is derived from the plant *Cannabis sativa* and has a longstanding history globally and in the United States. Its use has been documented for medical, spiritual, and recreational purposes. Cannabis is classified by the government as a Schedule I substance; however, within the past two decades, several states have passed legislation for medical and/or recreational programs, as this is allowable under federal law. Results from national surveys suggest an increase in the prevalence of cannabis use as well as changes in the perception of risk associated with its use. Prenatal cannabis use has been linked to adverse neonatal outcomes. Given evolving policies and changes in the prevalence of use, it is important to understand and synthesize the existing body of literature on prenatal cannabis use and its association with birth outcomes. A PubMed literature search performed in September 2019 yielded 21 articles on the prevalence of prenatal cannabis use and/or the association between prenatal cannabis use and birth outcomes for full-text review. Estimates of the prevalence of prenatal cannabis use ranged from less than one percent to approximately thirty percent in various prenatal populations across the United States and at different points in time. Adverse neonatal outcomes associated with cannabis use included decreased birthweight and decreased head circumference, though nine studies observed null

findings or a positive association between cannabis use and birth outcomes (prenatal use was associated with improved outcomes). Ten studies found a negative association between prenatal use and neonatal outcomes (use was associated with detrimental outcomes). Studies reviewed utilized multiple methods of cannabis detection (self-report, urine drug screen, hair sample), and several studies assessed prenatal cannabis use prospectively and/or longitudinally. However, eight studies only assessed cannabis use at the time of delivery and did not collect extensive information about the quantity, duration, and frequency of prenatal use. Given the inconsistency in and range of findings for both the prevalence of prenatal cannabis use and adverse birth outcomes, it is of public health importance to continue to investigate cannabis use among pregnant women, especially in the context of legislation which favors cannabis' legalization.

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Preface

To my peers at Pitt Public Health: It has been an honor to complete this journey with you. Best wishes for what lay ahead.

To my family and friends: The “thesis that’s not a thesis” is finally written – thanks for all your support and encouragement.

I would like to thank Ms. Helena VonVille for her assistance in conducting the literature review and Ms. Joanne Pegher for her assistance in formatting this essay, as well as Dr. Rosalie Pacula and Dr. Beau Kilmer for sharing their wisdom.

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1.0 Introduction

1.1 Overview

Cannabis has a long history of use for many purposes. A combination of recent changes in legislation, perceptions of risk/harm, and availability of cannabis may have impacted prevalence of cannabis use in the United States, including in pregnant women. This essay will uniquely provide both an overview of cannabis policy in the United States and a discussion of the evidence from a literature review of prenatal cannabis use and its impact on birth outcomes.

1.2 Definition and History of Cannabis

Cannabis sativa (C. sativa), commonly known in the United States as marijuana, is a flowering plant used for medicinal, recreational, and spiritual & religious purposes worldwide (Ren et al.); (Bonini et al.). Also called "cannabis" or "hemp plant," the term "marijuana" was not used until the 20th century (National Institute on Drug Abuse); cannabis is the preferred term in a professional context (Marcu). Historically, cannabis' primary use was for food, oil, clothing, and textiles (National Institute on Drug Abuse). For the purposes of this essay, cannabis includes all THC and CBD products. In North America, hemp was used for rope, clothing, and paper (Drug Enforcement Administration Museum & Visitors Center). Cannabis is believed to have been first domesticated in Central Asia or Southeast Asia (Bonini et al.). The first documented medical use of cannabis dates to approximately 5000 years ago (Bonini et al.). Under Emperor Chen Nung,

cannabis was prescribed for fatigue, rheumatism, and malaria (Bonini et al.). Cannabis has been recorded for medicinal use in other countries and cultures over history, including Assyria, ancient Greece, ancient Rome, Italy, and Arabic culture (Bonini et al.). However, cannabis was also documented to be associated with psychoactive effects. In 1932, cannabis was removed from the British Pharmacopoeia and banned for therapeutic use (Bonini et al.). In 1937 in the United States, possessing or transferring cannabis became federally illegal due to "The Marihuana Tax Act" (Bonini et al.). Over the past 80 years, the United States government has not formally changed its stance on cannabis as a controlled substance, although federal priorities regarding prosecution have changed over the past decade. Cannabis's longstanding history is complicated not only in the United States, but also globally. Federal and/or state support – or lack thereof – for cannabis use may create challenges in estimating its prevalence, availability, and potential impact on health outcomes.

1.3 Science and Pharmacology of Cannabis

1.3.1 Cannabinoids

Cannabinoids are the medical components of cannabis; over 100 cannabinoids exist (MacCallum and Russo). They are lipophilic with low water solubility (MacCallum and Russo). The most well-known cannabinoids are delta-9-tetrahydrocannabinol (THC), tetrahydrocannabinolic acid (THC-A), cannabidiol (CBD), and cannabinol (CBN). THC has psychoactive properties (MacCallum and Russo). It produces the distinct "high" feeling associated with cannabis and binds directly with cannabinoid receptors (MacCallum and Russo). For

symptom relief, THC has been shown to be efficacious to reduce nerve-related pain or spasms (Schrot and Hubbard); (MacCallum and Russo), as an anti-emetic (MacCallum and Russo), for spasm relief (MacCallum and Russo), as an appetite stimulant (MacCallum and Russo), and to reduce chronic cancer pain (Schrot and Hubbard). Conversely, CBD has non-intoxicating psychoactive properties (MacCallum and Russo). It is non-euphoric and binds indirectly with cannabinoid receptors (MacCallum and Russo). CBD is used for anti-inflammation (Schrot and Hubbard); (MacCallum and Russo), as an anti-psychotic (MacCallum and Russo), for neuro-protection (Schrot and Hubbard); (MacCallum and Russo), and for anti-convulsion in certain populations (United States Food and Drug Administration). In a pregnant population, women have reported using cannabis to mitigate severe nausea or morning sickness (Roberson, Patrick and Hurwitz). Women who report nausea and vomiting during pregnancy may also be more likely to use cannabis (Young-Wolff, Sarovar, Tucker, Avalos, et al.)

1.3.2 The Endocannabinoid System

The endocannabinoid system acts as a biological balancing system for the body, regulating physiological processes including appetite, pain and pleasure sensation, the immune system, coordination, cognition, and memory (Schrot and Hubbard). Endocannabinoids are neurotransmitters derived from arachidonic acid, or poly-unsaturated omega-6 fatty acid, in the body (Di Marzo et al.). They are fatty acid signaling molecules, acting as ligands for cannabinoid (CB) receptors (Di Marzo et al.). The cannabis plant produces phytocannabinoids, which act similarly to those produced by the body (MacCallum and Russo). Phytocannabinoids are produced most abundantly by the unfertilized female flower (MacCallum and Russo). While CBD and THC are primarily produced in nature, they mimic the effects of the endocannabinoids produced by the

body to regulate biological processes and provide symptom relief (Schrot and Hubbard). Because cannabinoids found in cannabis may compete with and/or mimic transmitters found in the body, they may disrupt normal body system functioning (Schrot and Hubbard).

CB receptors are members of the G-protein coupled receptor family (Di Marzo et al.). CB_1 receptors are primarily found in the brain and central nervous system, as well as in the cardiovascular, visual, and gastrointestinal systems (Schrot and Hubbard). CB_2 receptors are located primarily in the immune system in lymphatic tissue and the spleen, and have a lower affinity for THC compared to CB_1 receptors (Schrot and Hubbard).

1.3.3 Routes of Administration

Common routes of cannabis administration include: inhalation through smoking, using a ground-down female part of the cannabis plant that produces cannabinoids, or vaporizing, heating the cannabis plant at specific temperature under the point of combustion (451°F) without burning plant materials; oral, including edibles, tinctures, and lozenges, using ground-down flower; topical formulations, usually lotions, ointments, balms, or creams that are applied to specific areas of the body for local relief; and suppositories (MacCallum and Russo). If the plant is heated to very hot temperatures it will combust and burn entirely, allowing one to smoke cannabis, as opposed to vaporizing it (MacCallum and Russo). Different cannabinoids and terpenes have different points of activation, so depending on the temperature to which the plant is heated, the user will experience different effects and possible medical benefits. For example, Spindle et al. (2018) demonstrated that route of administration can impact strength of effect in a crossover trial of 17 healthy adults. Both smoking and vaporizing 10 mg and 25 mg of THC had significantly greater drug effects compared to the placebo (Spindle et al.). Furthermore, the effects of the 25-mg dose were greater

than those of the 10-mg dose, suggesting a dose-response relationship, and the effects from vaping were stronger than those from smoking, suggesting that different routes of administration may result in a different user experience (Spindle et al.). To note, the cannabis plant used by Spindle et al. had a greater concentration of THC relative to CBD, which may have impacted the subsequent physiological effects (Solowij). Thus, the concentrations of different cannabinoids in the product used may also play a role in the user's experience, which certainly has implications as CBD-rich products become increasingly available in today's market. When evaluating the potential benefits or harms associated with cannabis use, the route of administration, dose, and relative cannabinoid concentrations are all relevant and important factors to consider.

1.3.4 Contraindications and Side Effects

Though cannabis is widely used, and some physicians endorse its use for its therapeutic benefits for specific conditions such as multiple sclerosis, there are certain conditions for which its use is contraindicated. Those with psychotic illness are cautioned against using cannabis, as cannabis may increase risk of psychosis, especially in users who are already at-risk (Hasin); (National Academy of Sciences). There is mixed evidence on the benefit and/or detriment of cannabis use for anxiety (Hasin); (National Academy of Sciences). Even in conditions where cannabis may be recommended for medicinal purposes, recommending physicians should consider the potential side effects associated with cannabis use. For example, THC-rich products are most commonly associated with fatigue, nausea, dry mouth, and dizziness (MacCallum and Russo). They are also associated with ataxia or discoordination, tachycardia, and diarrhea, though these effects are rarer (MacCallum and Russo). Using a more balanced ratio of CBD and THC may ameliorate some of these adverse events (MacCallum and Russo). Additionally, the patient's

specific concerns and needs should be considered; a patient who suffers from insomnia may desire the drowsiness associated with THC, while another patient may not.

Specific to pregnancy, cannabis has been demonstrated to have a number of effects on the fetus including disruption of brain development before birth; smaller size at birth; greater risk of stillbirth; greater chance of premature birth, especially with concurrent cigarette and cannabis use; harm from secondhand cannabis smoke; and behavioral problems and trouble paying attention in school (The American College of Obsetricians and Gynecologists). Furthermore, the expecting woman is at risk for permanent lung injury from smoking; dizziness, making her a fall risk; impaired judgement, putting her at risk while driving; and lower levels of oxygen in body, which may lead to problems breathing (The American College of Obsetricians and Gynecologists). Given the potential harmful impacts of prenatal cannabis use on both the expecting woman and her fetus, synthesizing the available literature on this relationship may help to provide insights about the strength of association between prenatal cannabis use and infant outcomes.

1.4 Epidemiology of Cannabis Use

1.4.1 Prevalence and Perception of Risk

Epidemiology seeks to identify the distribution and determinants of disease. Studies such as Monitoring the Future and the Youth Risk Behavior Survey look specifically at youth. The National Survey on Drug Use and Health (NSDUH) is an annual, national survey on drug, tobacco, and alcohol use, as well as mental health, in the United States (Substance Abuse and Mental Health Services Administration "About the Survey"). Individuals ages 12 and older are eligible to

participate; approximately 70,000 people are interviewed annually for the survey (Substance Abuse and Mental Health Services Administration "About the Survey"). The survey collects self-reported data. NSDUH found that 53 million individuals living in the United States ages 12 and older used illicit drugs in 2018, representing approximately 20% of the population. Of these, 43.5 million (~16% of population) used cannabis in 2018. Among them, 18-25-year-olds used cannabis, and illicit drugs, at the greatest rate (38.7%, versus <20% for all other age groups) (Substance Abuse and Mental Health Services Administration "Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health"). Additionally, past-year cannabis use has significantly increased from 2002 (11.0%) to 2018 (15.9%, $p \leq 0.05$) (Substance Abuse and Mental Health Services Administration "Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health"). Though the NSDUH report did not differentiate between male and female patterns of cannabis use, other research suggests that men tend to use cannabis more often than do women, although women have shown more rapid progression from initial use to cannabis use disorder (Cuttler, Mischley and Sexton).

Illicit substance use is related to individuals' perception of risk/harm related to substance use. In response to a question on risk of drug use, 30.6% of people ages 12 or older responded smoking cannabis once or twice a week was a great risk. Approximately 70% (68.5%) responded that 4-5 drinks of alcohol daily was a great risk (Substance Abuse and Mental Health Services Administration "Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health"). These estimates that there are major discrepancies in terms of perceived risk associated with substance use among Americans, with fewer individuals perceiving weekly cannabis use as risky compared to daily alcohol use. Also,

the 2018 estimates of risk are lower than those from 2015-2017 (Substance Abuse and Mental Health Services Administration "Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health"). Prevalence of cannabis use has increased over the past two decades, while perception of harm associated with its use has decreased. It is also imperative to pay attention to certain populations, such as pregnant women, in order to determine the prevalence and health impacts of cannabis use.

Jarlenski et al. (2017) analyzed 2005-2015 NDSUH data. Across all female respondents, regardless of their pregnancy status or current cannabis use, there was an increase in the proportion of women who reported that cannabis use posed no risk, from 4.6% in 2005 to 19.0% in 2015 (Jarlenski et al.). Among pregnant women who did not report cannabis use in the past 30 days, 3.1% reported no risk of regular cannabis use in 2005 and 14.8% reported no risk in 2015 (Jarlenski et al.). Among pregnant women who reported cannabis use in the past 30 days, 23.7% and 62.6% stated no risk of regular cannabis use in 2005 and 2015, respectively (Jarlenski et al.). Thus, pregnant women are increasingly reporting no risk of cannabis use, as has been observed in the general population, especially among those who reported past-month use. These changes may provide insight into prevalence of use assessed in epidemiological research studies.

The Pregnancy Risk Assessment Monitoring System (PRAMS) is a joint collaborative effort between the Centers for Disease Control and Prevention (CDC) and state health departments (Centers for Disease Control and Prevention "About Prams"). PRAMS began in 1987 to “reduce infant morbidity and mortality by influencing maternal behaviors before, during, and immediately after pregnancy” (Centers for Disease Control and Prevention "About Prams"). Postpartum women are selected to participate via state birth certificate registry; surveys are sent out by mail” (Centers for Disease Control and Prevention "About Prams"). Currently, 47 states, New York City, Puerto

Rico, Washington, D.C., and the Great Plains Tribal Chairmen's Health Board participate in PRAMS (Centers for Disease Control and Prevention "Participating Prams Sites"). Data from several PRAMS studies are reported in the Results section.

1.4.2 Cannabis Use Disorder

Regular cannabis users may develop dependence or unhealthy patterns of use. The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) sets forth 11 criteria/symptoms for cannabis use disorder (Table 1) (American Psychological Association).

Table 1 Criteria for Cannabis Use Disorder

Symptoms	
Using cannabis in larger amounts or for longer than intended	Recurrent use in hazardous situations
Unsuccessful attempts to quit/cut down	Using despite negative effects (physical or psychological)
Spending excessive time in acquisition, using, or recovering from use	Needing more cannabis to obtain desired effect (tolerance)
Cravings and urges to use cannabis	Development of withdrawal symptoms, which can be relieved by taking more of the substance (withdrawal)
Continued use despite consistent social or interpersonal problems	Failure to fulfill major role obligations (work, school, home)
Important social, occupational, or recreational activities are given up or reduced because of cannabis use	

DSM-V incorporates severity of abuse/dependence. Individuals who meet 2-3 of the symptoms are classified as having mild cannabis use disorder; 4-6 symptoms represent moderate cannabis use disorder; 7 or more symptoms indicate severe cannabis use disorder (American Psychological Association).

The 2018 NSDUH categorized individuals as having cannabis use disorder based on the DSM-IV criteria. Substance use disorders were not classified independently from other disorders until DSM-III in 1980 (Lopez and Blanco). The DSM-IV, published in 1994 and used through 2013, was the first version of the manual to distinguish between abuse and dependence in substance use disorders (Lopez and Blanco). DSM-V, published in 2013, combines both abuse and dependence (Lopez and Blanco). DSM-IV included legal problems; DSM-V removed them but includes craving (Lopez and Blanco). DSM-IV also had fewer criteria required for an individual to achieve substance dependence. Given the DSM-IV criteria, approximately 4.4 million people, or 1.6% of the total population, had a cannabis use disorder in 2018; the subgroup with the greatest frequency of cannabis use disorder was 18-25-year-olds, at 5.9% (Substance Abuse and Mental Health Services Administration "Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health"). NSDUH results did not indicate the prevalence of cannabis use disorder among regular cannabis users. However, using other nationally representative data sources such as the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), Hasin and colleagues concluded that approximately 3 out of every 10 cannabis users had a cannabis use disorder in 2012-2013 (Hasin et al.). Compared to 2001-2002 results, prevalence of both past-year cannabis use and cannabis use disorders increased, although there was no increase in risk among users from 2001-2002 to 2012-2013 (Hasin et al.). The authors suggest that the increase in cannabis use disorders over time can thus be attributed to an increase in the number of cannabis users. Furthermore, as stated above, evidence suggested that women progress to dependence more quickly than do men (Cuttler, Mischley and Sexton). To provide context on other substance use disorders among users, the prevalence of DSM-IV alcohol use disorder among individuals who used alcohol within the past 12 months as assessed by the

NESARC, increased significantly from 2001-2002 (12.9%) to 2012-2013 (35.7%) (Grant et al.). The proportion of 12-month female alcohol users with DSM-IV alcohol use disorder increased significantly by 59.8%, from 8.2% in 2001-2002 to 13.1% in 2012-2013 (Grant et al.). Overall, the prevalence of substance use disorders among users appears to be greater over time. Identifying patterns in cannabis use may help to facilitate a better understanding available data on cannabis use. Given the fairly recent change from DSM-IV to DSM-V, especially in light of the recency of some cannabis research, it is imperative to consider the time of publication and the DSM classification used to define CUD. Recent research has also focused on whether legalization of recreational cannabis has impacted rates or risk of CUD (Lopez and Blanco). Section 1.5.3 provides information on state-specific cannabis policies.

1.5 Legality of Cannabis

Federally, cannabis is illegal to use, sell, or distribute. Through the Controlled Substances Act (21 U.S.C. § 811), the federal government does not differentiate between medical and recreational cannabis use (Americans for Safe Access). Cannabis is a Schedule I drug (on a classification scheme from I-V, with I being the most restrictive), indicating that it has a strong potential for abuse and/or dependence and no currently-accepted medical use (United States Drug Enforcement Administration). Typically, punitive measures are only taken against individuals with large quantities of cannabis (Americans for Safe Access). Physicians and healthcare providers are authorized by individual states to *certify a qualifying medical condition* or make a *recommendation for medical cannabis* to eligible patients; because they are not prescribing cannabis, no legal

recourse against these providers is possible (Americans for Safe Access). State-specific medical cannabis programs are allowable under federal law (Americans for Safe Access).

1.5.1 Federal Government Position

Between 2009 and 2018, the federal government issued five memos with updates to the federal government's priorities concerning cannabis. Each subsequent memo references the previous one(s), which helps provide a natural flow of the federal government's stance on and response to (medical) cannabis. Figure 1 summarizes chief statements and takeaways from each of the five memos. In 2009, the United States Department of Justice issued guidance on federal tolerance for state medical cannabis programs and laws. The stance was such that it was not an efficient use of federal resources to prosecute individuals such as terminally ill cancer patients who use cannabis therapeutically. To note, this memorandum is not the same as legalization; rather, it was meant to appropriately guide federal action (Odgen). In 2011, Deputy Attorney General James M. Cole went on to state that "Persons who are in the business of cultivating, selling or distributing marijuana, and those who knowingly facilitate such activities, are in violation of the Controlled Substances Act, regardless of state law," underscoring that enforcing the Controlled Substances Act remained a federal government priority (Cole "Guidance Regarding the Ogden Memo in Jurisdictions: Seeking to Authorize Marijuana for Medical Use").

In 2013, the United States Deputy Attorney General James M. Cole released a memo, issuing eight guidelines for federal prosecutors to follow in terms of federal enforcement priorities (Cole "Guidance Regarding Marijuana Enforcement"): 1) Preventing the distribution of marijuana to minors; 2) Preventing revenue from the sale of marijuana from going to criminal enterprises, gangs or cartels; 3) Preventing the diversion of marijuana from states where it is legal under to

state law in some form to other states; 4) Preventing state-authorized marijuana activity from being used as a cover or a pretext to traffic other illegal drugs or other illegal activity; 5) Preventing violence or the use of firearms in cultivation and distribution of marijuana; 6) Preventing drugged driving and the exacerbation of other adverse public health consequences associated with marijuana use; 7) Preventing the growing of marijuana on public lands and the attendant public safety and environment dangers posed by marijuana production on public lands; and 8) Preventing marijuana possession or use on federal property.

The Department of Justice has historically left cannabis prosecution to state or local law enforcement agencies. States can help facilitate execution of federal laws through their regulatory processes (ex: prohibiting minors' access to marijuana, as outlined above) (Cole "Guidance Regarding Marijuana Enforcement"). To further underscore this opinion, Deputy Attorney General James M. Cole's 2014 memo stated that federal prosecutors will actively find and penalize people or businesses with large financial violations of the Controlled Substances Act, and may face criminal liability depending on the activities in which they engaged (Cole "Guidance Regarding Marijuana Related Financial Crimes"). Lastly, the 2018 memo from Jefferson B. Sessions, III, US Attorney General (U.S.C. § 841 *el seq*) withdrew federal support for cannabis enforcement: "Given the Department's well-established general principles, previous nationwide guidance specific to cannabis enforcement is unnecessary and is rescinded, effective immediately" (Sessions). The federal government's position on cannabis' legality have implications for public health practice.

Figure 1 Timeline Representing Chief Statements and Takeaways from the Department of Justice Memos

1.5.2 Implications for Cannabis Research

Cannabis research is greatly impacted by federal policy and restrictions. Because federal funding for cannabis research is limited, properly designed and rigorous epidemiologic studies are scarce. In 2017, the National Academy of Sciences, Engineering, and Medicine (NAS) issued a report titled *The Health Effects of Cannabis and Cannabinoids: Committee's Conclusions*, based on the review of over 10,000 scientific abstracts from cannabis health research. As such, it is considered the current "gold standard" review, though it is somewhat limited because most of the research evaluated is dated prior to 2017. Since the physiological effects of cannabis are an emerging area of research, this report may not accurately capture the most recent research, trends, and conclusions, though it provides a useful foundation/starting point.

The report included a section on research, funding, and program execution. NAS identified several challenges and barriers to cannabis/cannabinoid research, including regulatory barriers (i.e., cannabis is a Schedule I substance); lack of ability to access the necessary quality, quantity and type of cannabis product to answer specific research questions; insufficient and/or a lack of

diversity in funding to support research; and lack of standardization in research methodology (National Academy of Sciences). To address these barriers, the NAS also included recommendations for developing a comprehensive evidence base on both the short- and long-term health effects of cannabis use: support from a variety of organizations (such as government, industry, academic institutions, and non-profit) for a national cannabis research agenda; federal support for a workshop to develop research standards and benchmarks; implementation of federal public health surveillance systems and state-based public health surveillance; and creating a committee of experts to create an evidence-based report to address barriers to research and propose strategies to promote better research (National Academy of Sciences).

1.5.3 State Policies on Cannabis Use

There is considerable variation among state-specific cannabis policies. Generally, states have legalized cannabis for medical purposes only, legalized cannabis for all uses (both medicinal and recreational), or have no policy supporting cannabis use at all. In 1996, California became the first state to implement a medical cannabis policy (National Conference of State Legislatures); (DISA Global Solutions). As of August 2019, cannabis is fully legal in 12 states (with pending legislation in Illinois, effective 2020) and of mixed legality in 27 states (with pending legislation in Hawaii, effective 2020) (Appendix B; Figure 2). A complete listing of state-specific policies, including legal and decriminalization status and year of legislation, can be found in Appendix B.

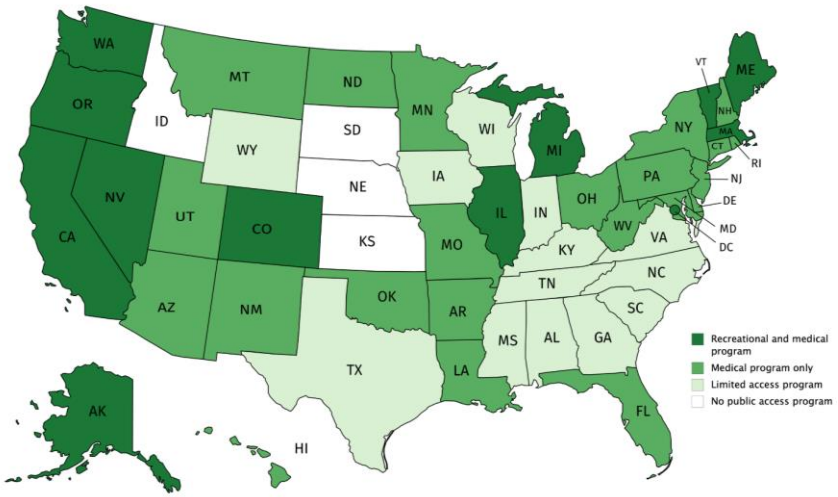

Figure 2 Legality of State Cannabais Programs, 2019

Created by author using https://mapchart.net/usa.html and http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx.

Approximately two-thirds (22 states) of medical legislation became effective during or after 2007 (Figure 3); recreational legislation became effective during or after 2012 (Figure 4). Cannabis is fully decriminalized in a minority of states (n=12) but is fully *or* partially decriminalized in about half of all states (n=27) (Figure 5). When evaluating different states' policies, it is important to understand and consider nuances unique to each state and not to simply look at cannabis' legal status in a particular state (Klieger et al.). Because policy does not always translate directly to practice, when reviewing literature on cannabis policy, one should consider whether the studies looked at cannabis policy or cannabis practice, which may differ from what is allowed by law (Klieger et al.). A lack of federal support for cannabis may create challenges at the state-level in terms of implementing a regulatory framework and subsequently ensuring the health of each state's constituents (Klieger et al.). Appendix C summarizes both federal and state approaches to regulating medical cannabis, as outlined in Klieger et al. (2017).

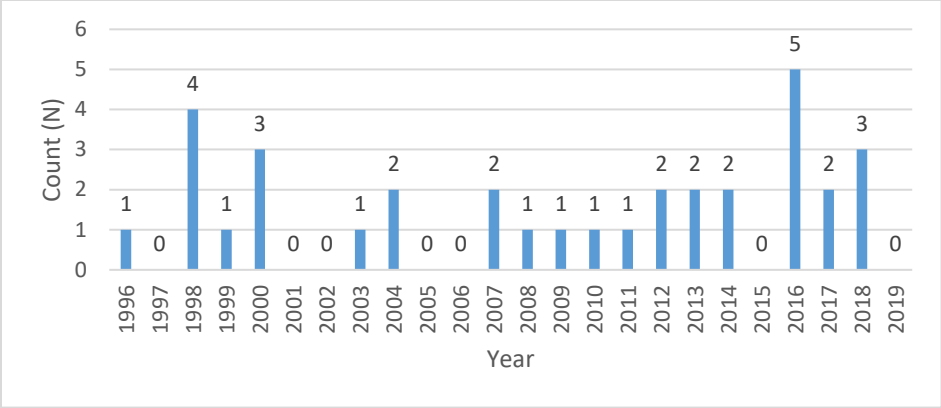

Figure 3 Number of States Which Passed Legislation for a Medical Program, By Year (1996-2019)

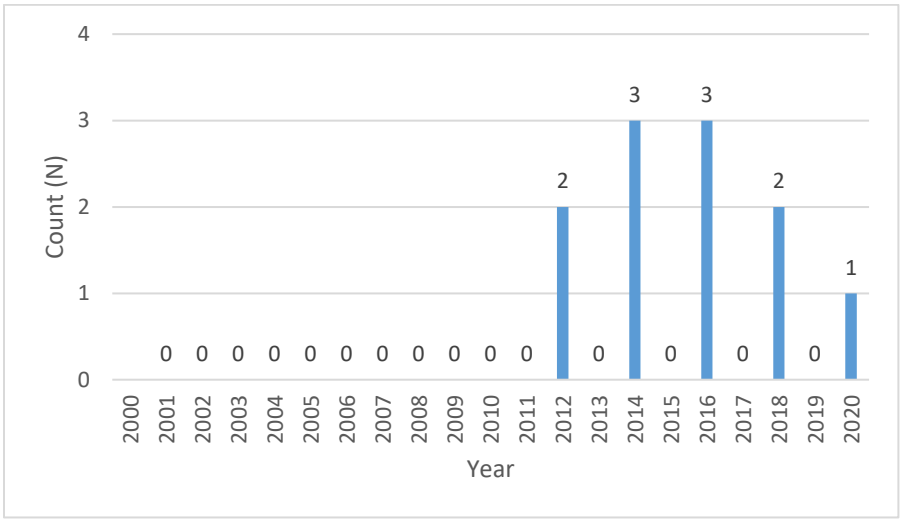

Figure 4 Number of States Which Passed Legalization for a Recreational Program, By Year (2000-2020)

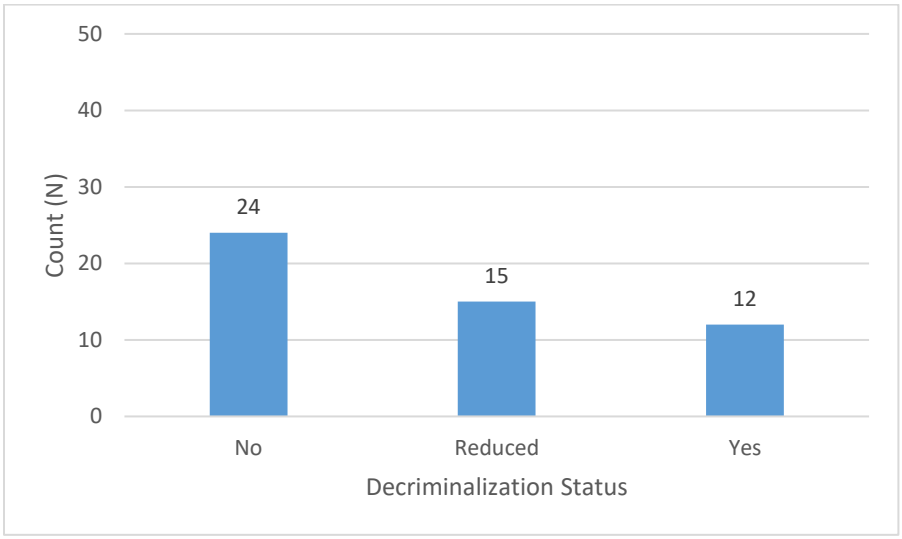

Figure 5 Number of States in which Cannabis is Decriminalized

1.6 Cannabis Use in Pregnancy

1.6.1 Surgeon General Advisory Report

In August 2019, the Surgeon General released an advisory report on prenatal cannabis use and the developing brain. A primary concern is the change in cannabis' THC potency over time. THC concentration tripled from 1995 to 2014, from 4% to 12% (ElSohly et al.). Additionally, prevalence of cannabis use during pregnancy doubled, from 3.4% in 2002 to 7% in 2017 (Volkow et al.). Surgeon General VADM Jerome Adams wrote, "The American College of Obstetricians and Gynecologists holds that '[w]omen who are pregnant or contemplating pregnancy should be encouraged to discontinue marijuana use. Women reporting marijuana use should be counseled about concerns regarding potential adverse health consequences of continued use during pregnancy.'" ("Committee Opinion No. 722: Marijuana Use During Pregnancy and Lactation," 2017). As not all women may not be aware of the possible implications of prenatal cannabis use, it is imperative to educate this population to support them in being as healthy as possible during, as well as after, pregnancy. Both prevalence of prenatal cannabis use and cannabis potency have increased in recent years. These changes may have potential implications on adverse birth outcomes, so quantifying and addressing them is critical for ensuring the health of mothers and babies alike. The report also highlights the need for additional research on prenatal cannabis use.

1.6.2 National Academy of Sciences, Engineering, and Medicine Report

Additionally, the 2017 NAS report included a section on maternal and child outcomes. The report concludes that there is:

"Substantial evidence of statistical association between maternal cannabis smoking and lower birthweight of offspring (10-2);" (p. 253)

"Limited evidence of statistical association between maternal cannabis smoking and pregnancy complications for the mother (10-1); admission of infant to NICU (10-3);" (p. 254)

Insufficient evidence to support or refute statistical association between maternal cannabis smoking and later outcomes in offspring (10-4);" (p. 260) and

"No or insufficient evidence to support or refute a statistical association between cannabis use and subsequent risk of developing [various cancers] (parental cannabis use) (5-6)" (p. 156) (National Academy of Sciences).

Based on these conclusions, it appears that babies born to mothers who used cannabis during pregnancy may be at an increased risk for adverse birth outcomes. Yet, there does not appear to be a clear consensus; thus, further research and critique of available evidence is needed.

1.7 Public Health Significance

Cannabis use has gained considerable attention in the media. Changes in state-specific policy, new and existing research findings, and updates to federal policy and priorities will continue to play an important role in the accessibility and legality of cannabis, as well as the potential impacts associated with its use prenatally. Additionally, findings from several domestic and international epidemiological studies support the association between prenatal cannabis use and adverse birth outcomes. However, some results are equivocal and there are limitations to existing research methodology, warranting further investigation on this association.

2.0 Objectives

The objectives of this essay were to: 1) create a compendium of state-specific cannabis policy; and 2) review the literature on the prevalence of cannabis use in pregnancy and the impact of prenatal use on neonatal outcomes. Together, these objectives will serve the end goal of providing evidence for how changes in policy potentially impact changes in cannabis use over time, critiquing the literature with an epidemiological perspective.

3.0 Methods

3.1 Search Overview

PubMed (National Library of Medicine) was used for the literature review. The University of Pittsburgh Health Sciences Library has institutional access to *PubMed*, allowing for optimal retrieval of literature. A health sciences librarian with experience in systematic reviews assisted with developing of and facilitating the execution of the search, which was conducted on September 25, 2019. A combination of MeSH terms and title, abstract, and keywords were used to develop the initial *PubMed* search. *EndNote* (publisher: Clairvate Analytics) was used to store all citations found in the search process. An Excel workbook designed by a health sciences librarian was used to track search strategies and results (VonVille). Table 2 breaks down the line-by-line search conducted in PubMed to retrieve titles and abstracts for the literature review. Because the researcher can only read and interpret scholarly literature in English, the search was restricted to this language only. Additionally, the research was focused on identifying state-specific cannabis policies and prenatal cannabis use studies in the United States; therefore, the geographic region was restricted to the United States.

Table 2 Line-by-line Search in PubMed to Retrieve Titles and Abstracts for Literature Review on the Association Between Prenatal Cannabis Use and Adverse Neonatal Outcomes

Line number	Search string
1	Cannabis[mesh:noexp]
2	(marijuana[tiab] OR marihuana OR Cannabis[tiab])
3	#1 OR #2
4	Pregnancy Trimesters[mesh:noexp] OR Pregnancy Outcome[mesh:noexp] OR Pregnancy Trimester, Third[mesh:noexp] OR Pregnancy, Unplanned[mesh:noexp] OR Pregnancy[mesh:noexp] OR Pregnancy Trimester, First[mesh:noexp] OR Pregnancy, High-Risk[mesh:noexp] OR Pregnancy Trimester, Second[mesh:noexp] OR Pregnancy Complications[mesh:noexp] OR pregnant women[mesh]
5	pregnan*[tiab] OR perinatal[tiab] OR prenatal[tiab]
6	#4 OR #5
7	#3 AND #6
8	#7 AND english[la]
9	(#8 AND humans[mesh]) OR (#8 not animals[mesh:noexp])
10	((#9 AND (north america[MESH:NOEXP] OR united states[MESH])) OR (#9 NOT (africa[MESH] OR asia[MESH] OR australia[MESH] OR canada[MESH] OR europe[MESH] OR south america[MESH])))

3.2 Exclusion Criteria

A comprehensive list of exclusion criteria to guide title and abstract screening was developed, resulting in 13 exclusion criteria used during the screening (Table 3):

Table 3 Exclusion Criteria for Title and Abstract Screening for Articles Examining the Association Between Prenatal Cannabis Use and Adverse Neonatal Outcomes

Cannabis not used or polysubstance use during pregnancy
Cannabis use at time other than pregnancy
Population not described clearly
Not an observational study
Study setting not US (50 states & D.C.)
Time frame not defined
Did not study humans
Women not of reproductive age
Longitudinal study without birth outcome data
Not an original study (editorial, comment, review, meta-analysis) or research letter
Cannabis use not primary exposure – focused on other comorbidity (ex: HIV, MS)
Focus on scientific tools (detection, etc.) or methodology
Other

To note, the exclusion criterion "Cannabis not used or polysubstance use during pregnancy" refers to studies which were focused on overall substance use and did not *specifically* identify patterns of cannabis use and its possible effects on birth outcomes. Randomized controlled trials were not included in order to assess prenatal cannabis use organically; that is, to understand its prevalence in a real-world setting. After all titles and abstracts were screened by the researcher during the initial review, full-text items were retrieved and screened using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

3.3 Overview of Literature Search

The PubMed search yielded 1167 titles and abstracts, of which 1048 were removed due to the exclusion criteria described previously. Due to the large number of potential full-text items identified (N=119), two additional exclusion criteria were added during full-text review, in addition to the 13 criteria listed above – "Adolescent population sole focus" and "Focus on pregnancy outcomes, not birth outcomes." This additional restriction helped to tighten the focus of the research question. Of the remaining 119 titles and abstracts, 21 were deemed appropriate for full-text review, as they did not meet any of the exclusion criteria. Figure 6 depicts how many titles/abstracts and full-text articles were included, as well as how many were excluded and why.

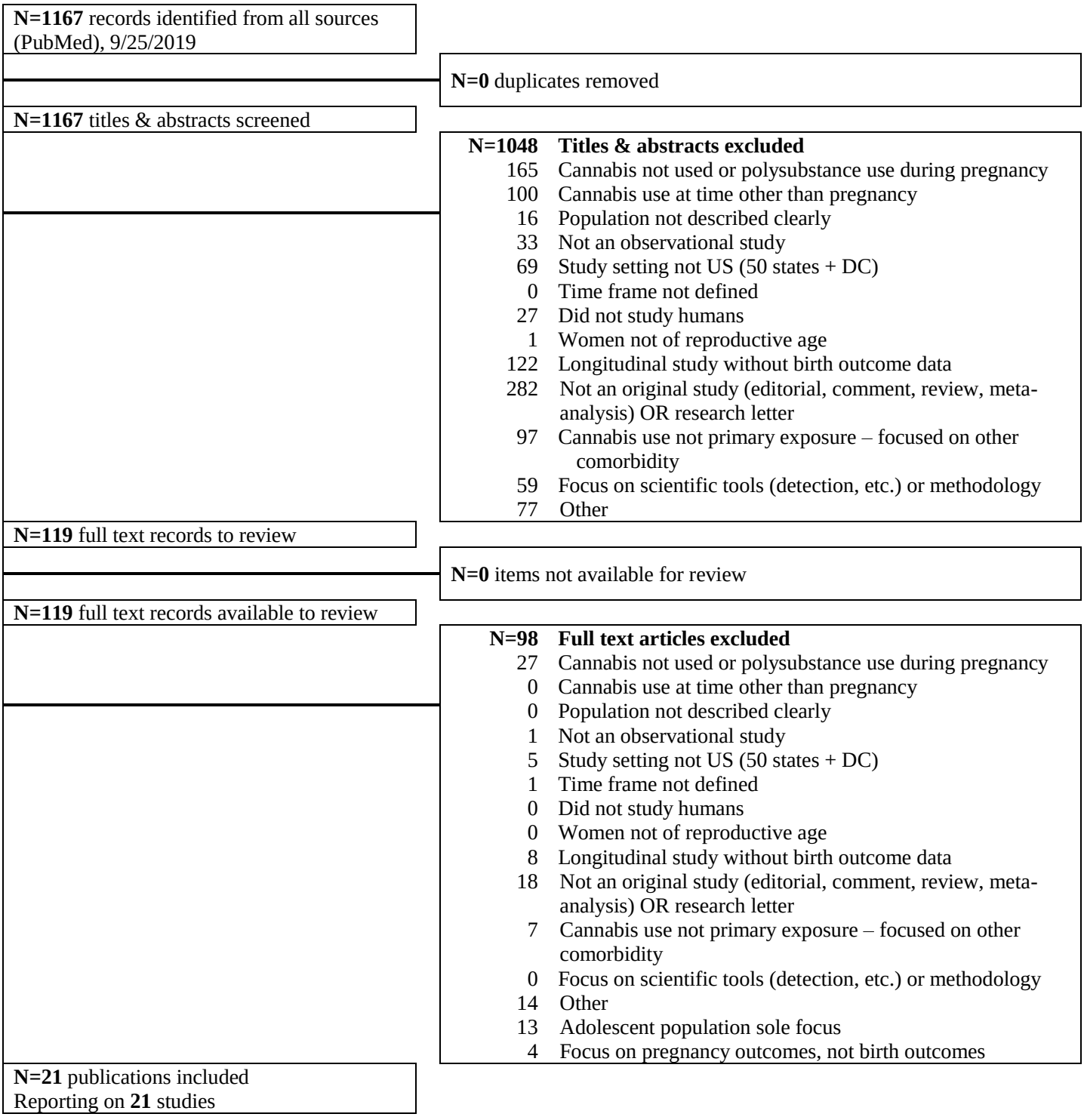

Figure 6 Number of Articles Included and Excluded from Title and Abstract Screening and Full-text Review on Association Between Prenatal Cannabis Use and Adverse Neonatal Outcomes

Most of the 1,048 titles and abstracts excluded were because they were not original studies or were a research letter (N=282), cannabis was not used or polysubstance use occurred during pregnancy (N=165), the study was not focused on neonatal outcomes explicitly (i.e., was longitudinal following birth) (N=122), or cannabis was used at a time other than pregnancy (N=100). Similarly, of the 98 full text articles excluded, 27 were excluded because cannabis was not used or polysubstance use occurred during pregnancy and 18 were excluded because they were not original studies or were a research letter. Based on the title and abstract alone, it was not clear that a few studies (n=5) did not take place in the United States; upon full-text review, this was made clear and the studies were subsequently excluded (Figure 6).

4.0 Results

4.1 Study Characteristics

Of the 21 studies identified, 12 (57.1%) controlled for maternal tobacco/cigarette use and 9 (42.9%) did not. In terms of geographic scope, 17 (81.0%) were state-level and 4 (19.0%) were national-level. Of the 17 studies at the state-level, 1 was in Massachusetts, Connecticut, Texas, Alaska, Vermont, Washington State, Missouri, or California; 2 were in Ohio, Hawaii, Maryland, or Pennsylvania; and 3 were in Colorado. Some studies were based in more than one state but were not focused on all 50 states plus D.C (i.e., the nation). A minority of studies (N=2, 9.5%) focused on birth outcomes alone, both of which were at the state level; 8 studies (38.1%) focused on prevalence of prenatal cannabis use alone, 5 state-level and 3 national-level; and 11 studies (52.3%) identified both birth outcomes and prevalence of prenatal cannabis use (10 state-level and 1 national-level) (Appendix D). Publication dates ranged from 1983 to 2019, with a majority of articles (N=18, 85.7%) written within the past 10 years (2010-present) (Figure 7). Three scholars (Metz, Coleman-Cowger, and Ko) were first authors on 2 studies each, for a total of 6 articles written by 1 of 3 first authors (Figure 8). As seen in Figure 9, the majority of studies were cross-sectional (N=10) or longitudinal retrospective (N=8).

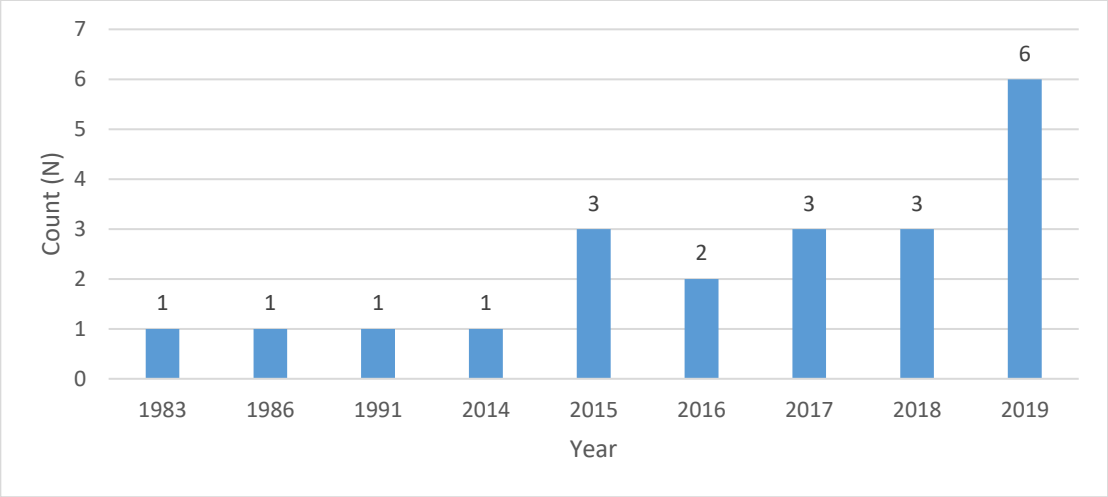

Figure 7 Number of Articles Assessing Prenatal Cannabis Use and Adverse Neonatal Outcomes Reviewed, By Year of Publication

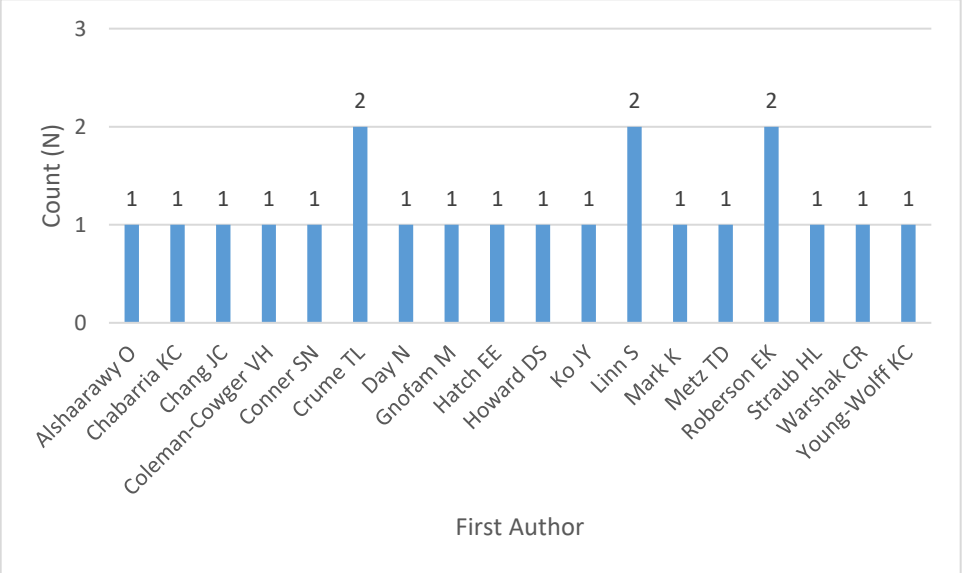

Figure 8 First Authors and Number of Articles Assessing Prenatal Cannabis Use and Adverse Neonatal Outcomes Written By Each First Author

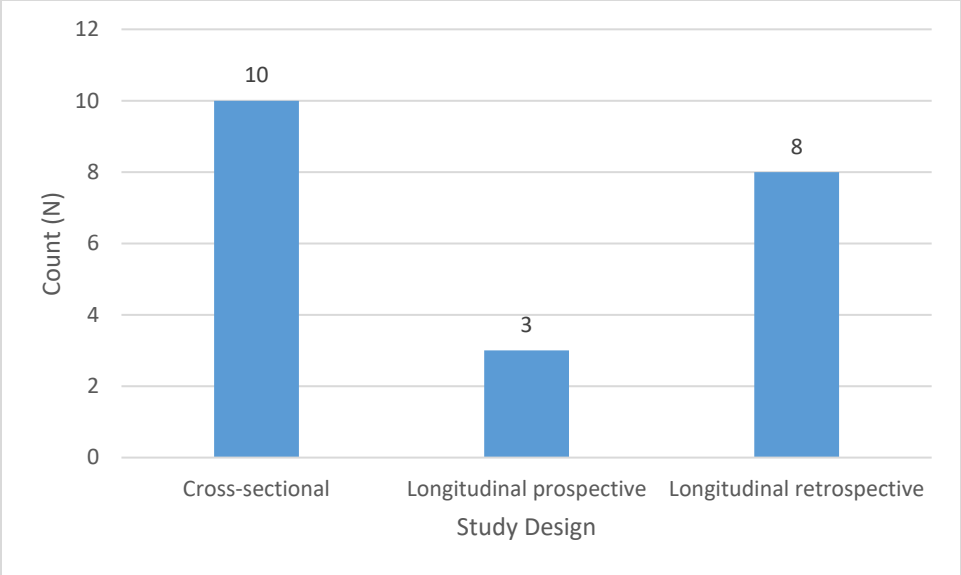

Figure 9 Breakdown of Articles Assessing Prenatal Cannabis Use and Adverse Neonatal Outcomes Reviewed, By Study Design

4.2 Summary of Findings from Studies

Study authors, year of publication, sample characteristics, and results are summarized in Appendix D. Studies are organized from earliest to most recent date of publication; studies published in the same year are organized alphabetically by first author.

4.2.1 Prevalence

Prenatal cannabis users were identified as younger (Linn et al.); (Ko, Farr, et al.); (Metz, Silver, et al.); (Young-Wolff, Sarovar, Tucker, Conway, et al.); (Warshak et al.); (Chabarria et al.), nonwhite (Linn et al.); (Young-Wolff, Sarovar, Tucker, Conway, et al.); (Howard et al.); (Crume et al.); (Hatch and Bracken); (Ko, Tong, et al.); (Conner et al.); (Crume et al.); (Hatch and

Bracken); (Ko, Tong, et al.); (Conner et al.); (Day et al.); (Coleman-Cowger, Oga, et al.), less educated (Linn et al.); (Crume et al.); (Hatch and Bracken); (Roberson, Patrick and Hurwitz); (Mark, Desai and Terplan); (Ko, Tong, et al.); (Metz, Allshouse, et al.), single/not married (Crume et al.); (Ko, Tong, et al.); (Day et al.), having/having had an unplanned pregnancy (Linn et al.), tobacco and/or other substance co-users (Crume et al.); (Hatch and Bracken); (Mark, Desai and Terplan); (Ko, Tong, et al.); (Straub et al.); (Conner et al.); (Metz, Allshouse, et al.); (Day et al.); (Warshak et al.); (Chabarria et al.), of lower income/socioeconomic (SES) status (Ko, Farr, et al.); (Young-Wolff, Sarovar, Tucker, Conway, et al.); (Roberson, Patrick and Hurwitz); (Ko, Tong, et al.); (Straub et al.); (Day et al.), and unemployed (Mark, Desai and Terplan); (Coleman-Cowger, Oga, et al.). Prenatal use was found to be greatest in the first trimester (Coleman-Cowger, Pickworth, et al.); (Alshaarawy and Anthony), with estimates up to 8.1% in 2017 (Alshaarawy and Anthony). A majority of women (96%) who used cannabis during pregnancy also reported using cannabis before pregnancy (Young-Wolff, Sarovar, Tucker, Conway, et al.) (Appendix D).

Methods of evaluating prenatal cannabis use included self-report (Linn et al.); (Alshaarawy and Anthony); (Coleman-Cowger, Pickworth, et al.); (Chang et al.); (Metz, Silver, et al.); (Ko, Farr, et al.); (Young-Wolff, Sarovar, Tucker, Conway, et al.); (Crume et al.); (Hatch and Bracken); (Gnofam et al.); (Roberson, Patrick and Hurwitz); (Mark, Desai and Terplan); (Ko, Tong, et al.); (Conner et al.); (Metz, Allshouse, et al.); (Day et al.); (Metz, Allshouse, et al.), bio-detection, including urine drug screen (UDS) or urine tox screen, (Chang et al.); (Howard et al.); (Gnofam et al.); (Mark, Desai and Terplan); (Conner et al.); (Straub et al.); (Coleman-Cowger, Oga, et al.); (Coleman-Cowger, Oga, et al.), meconium (Howard et al.); (Gnofam et al.), and THC-A umbilical cord homogenate sample (Metz, Silver, et al.). Evidence suggests that prevalence of prenatal cannabis use has increased over the past two decades. In a secondary data analysis of cross-

sectional NSDUH data of over 380,000 pregnant women from 2003 to 2017, Alshaarawy & Anthony (2019) found that prenatal cannabis use during the first trimester increased from 5.6% in 2002 to 8.1% in 2017. Similarly, Young-Wolff et al. (2019) showed that from 2009 to 20017, use increased from 2.07% to 3.38% ($p<0.001$). This study was a longitudinal evaluation of cross-sectional data from nearly 280,000 women representing over 360,000 pregnancies in California between 2009 and 2017 (Young-Wolff, Sarovar, Tucker, Conway, et al.). While prevalence of cannabis use increased over time, some have noted a decrease in cigar and cigarette use, an important correlate of cannabis use, over time (Coleman-Cowger, Pickworth, et al.). Various timepoints (i.e., past-year use, first trimester use, etc.) and categories (i.e., frequent vs. never user) of prenatal cannabis use were used across studies (Appendix D).

In a retrospective medical record review of 2,173 singleton births from 2013 to 2014, Howard et al. (2019) assessed prenatal cannabis use during pregnancy and at delivery using UDS and found that 115 of 2,173 (5.3%) pregnant women in the study who were screened had positive results both initially (during pregnancy) and at delivery. Other estimates ranged from 2.6% via self-report (Roberson, Patrick and Hurwitz) to upwards of 20% from UDS (Straub et al.). Also, within prenatal users, prevalence varied by trimester. For example, Crume et al. (2018) noted that 4.8% (95% CI 4.0-5.9) of women who gave birth in Colorado between 2014 and 2015 as part of a cross-sectional study using a stratified random sample used during the first trimester, compared to 2.4% (95% CI 1.8-3.1) in the third, with an overall prevalence of 5.7% (95% CI 4.8-6.8). Mark et al.'s (2016) retrospective cohort study of 396 pregnant women who delivered at urban clinics in Maryland between 2006 and 2010 estimated trimester 1 prevalence at 21.8%, trimester 2 prevalence at 17.5%, and trimester 3 prevalence at 0%. Day et al. (1991) looked at over 1,000 women in the Pittsburgh area between 1983 and 1986 as part of a longitudinal study; cannabis use

decreased over the first trimester from 24% to 12%, with an estimated prevalence of 7% in the second and third trimesters. Approximately 10% of women who delivered live singleton births between 1980 and 1982 in a prospective study based in Connecticut used cannabis regularly (5.4%) or occasionally (4.1%) (Hatch and Bracken). In a secondary analysis of Hawaii PRAMS data, Roberson et al. (2014) showed that over one-fifth (21.2%) of women reported severe nausea during pregnancy. Reporting severe nausea during pregnancy was associated with a greater prevalence of prenatal cannabis use. Approximately 4% (3.7%) of women who reported severe nausea during pregnancy used cannabis during pregnancy, compared to 2.3% of women who did not report severe nausea (prevalence ratio=1.63, 95% CI 1.08-2.44).

While Gnofam et al. (2019) did not conduct a longitudinal study, the authors evaluated prevalence of prenatal cannabis use at any time during pregnancy both before and after the commencement of Colorado's first recreational cannabis sales in January 2014 via a retrospective cohort study. They found an increase in both the frequency of prevalence cannabis use over the legalization period (from 3.7% in 2012 to 5.9% in 2015) and the odds of cannabis use post-legalization (OR=1.8, 95% CI 1.2-2.5). Similarly, they noted an increase in the prevalence and the odds (adjusted OR=1.9, 95% CI 1.3-3.1) of fetal growth restriction post-legalization in a model adjusted for ethnicity and other drug (including tobacco) use, with no other significant differences in neonatal outcomes (Gnofam et al.).

Chang et al. (2017) compared agreement between UDS and spontaneous self-report of prenatal use to physicians in an observational study of 422 pregnant women who visited outpatient prenatal clinics in Pittsburgh between 2011 and 2014. Of those who self-reported prenatal use, 87.0% also has a positive UDS; however, 46% of women who had a positive drug screen did not self-report use. This study estimated overall prevalence of cannabis use, regardless of detection

method, at around 25%. Of importance, this study looked at unsolicited reporting, compared to other studies which actively inquire about cannabis use and promise anonymity and confidentiality. Metz et al. (2019) used the neonate's umbilical cord from 116 pregnant women in Colorado during 2016 as part of a cross-sectional study to detect the presence of THC-A as a proxy for use. Prevalence estimates from cord homogenate assays were greater than those self-reported by participants to their physicians, with no substantial agreement between measures (Metz, Silver, et al.). Nearly one-quarter (22.4%) of participants had THC-A levels greater than the limit of detection and 10.3% had THC-A levels greater than the limit of quantification (Metz, Silver, et al.), indicating elevated levels of use during the third trimester of pregnancy in Colorado. However, only 2.6% of women self-reported prenatal use to their provider (Metz, Silver, et al.).

Cross-sectional prevalence estimates ranged widely between studies. Approximately 7% of participants reported occasional prenatal use (Linn et al.), 3.9%-6.0% reported past-month use (Ko, Farr, et al.); (Alshaarawy and Anthony); (Metz, Silver, et al.), 2.5% reported use at any point during pregnancy (Young-Wolff, Sarovar, Tucker, Conway, et al.). One-fifth of participants in Chang et al. (2017) reported current use. Young-Wolff et al. (2019) found that the greatest increase in prenatal use was for daily use, up from 1.95% in 2009 to 3.38% in 2017. This study was conducted on a California population. California legalized cannabis for all uses in 2003 (National Conference of State Legislatures); (DISA Global Solutions). In terms of cannabis abuse and/or dependence, pregnant users were more likely to demonstrate these behaviors compared to nonpregnant users (Ko, Farr, et al.); (Alshaarawy and Anthony). Lastly, in a secondary data analysis of over 90,000 pregnant women from NSDUH data between 2007 and 2012, researchers found that approximately 70% of all cannabis users, regardless of pregnancy status, perceived occasional cannabis use as being slightly or not at all risky (Ko, Farr, et al.).

Table 4 summarizes state-specific estimates from the identified studies that assessed prenatal cannabis use at the state-level, as well as national-level estimates from the studies reviewed which assessed prenatal cannabis use across the United States.

Table 4 Summary of State-Specific and National Prevalence Estimates of Prenatal Cannabis Use

State (# of studies)	Year(s) Data Collected (chronologically within state)	Estimated Prevalence
Alaska (1)	2009-2011	6.6%
California (1)	2009-2017	2.5%
Colorado (3)	1. 2014-2015 2. 2012-2015 3. 2016	5.7% 3.7% (2012); 5.9% (2015) 2.6%
Connecticut (1)	1980-1982	5.4%
Hawaii (2)	1. 2009-2011 2. 2009-2011	6.0% 2.8%
Maryland (2)	1. 2009-2016 2. 2017	29.3% 12.1% (past-month use)
Massachusetts (1)	1977-1980	7.1%
Missouri (1)	2004-2008	8.4%
Ohio (2)	1. 2008-2011 2. 2013-2014	5.6% 22.6%
Pennsylvania (2)	1. 1983-1986 2. 2011-2014	24% (1983); 12% (1986) – trim 1 20.0%
Texas (1)	2011-2015	0.88%
Vermont (1)	2009-2011	5.5%
Washington State (1)	2011-2016	23.7%
National (4)	1. 2006-2018 2. 2006-2016 3. 2007-2012 4. 2002-2017	2.7% 3.1% (2006); 5.2% (2016) 3.9% (past-month use) 5.6% (2002-05); 8.1% (2014-17); 4.0% (overall)

Table 5 Summary of State-Specific Prevalence Estimates of Prenatal Cannabis Use and State-Specific Legality of Cannabis

State (# of studies), alphabetically	Year(s) Data Collected (chronologically within state)	Legal Status	Year of Legislation (# pieces of legislation in year)	Study done pre, post, or during legalization	Estimated Prevalence
Alaska (1)	2009-2011	Fully legal	1998 1999	Post	6.6%
California (1)	2009-2017	Fully legal	1996 2003	Post	2.5%
Colorado (3)	1. 2014-2015 2. 2012-2015 3. 2016	Fully legal	2000	Post	5.7% 3.7% (2012); 5.9% (2015) 2.6%
Connecticut (1)	1980-1982	Mixed	2012	Pre	5.4%
Hawaii (2)	1. 2009-2011 2. 2009-2011	Mixed	2000	Post	6.0% 2.8%
Maryland (2)	1. 2009-2016 2. 2017	Mixed	2003 2011 2013 (2) 2014	During and post	29.3% 12.1% (past-month use)
Massachusetts (1)	1977-1980	Fully legal	2012 2013	Pre	7.1%
Missouri (1)	2004-2008	Mixed	2018	Pre	8.4%
Ohio (2)	1. 2008-2011 2. 2013-2014	Mixed	2016	Pre	5.6% 22.6%
Pennsylvania (2)	1. 1983-1986 2. 2011-2014	Mixed	2016	Pre	24% (1983); 12% (1986) – trim 1 20.0%
Texas (1)	2011-2015	Mixed	2015 2019 (2)	Pre and during	0.88%
Vermont (1)	2009-2011	Fully legal	2004 2007 2011 2018	During and post	5.5%
Washington State (1)	2011-2016	Fully legal	2009 2010 2011	During and post	23.7%

4.2.2 Birth Outcomes

Appendix A is a glossary with definitions and abbreviations of the birth outcomes reported in this essay, as well as statistical measures. With regards to birth outcomes, odds of small for gestational age (SGA) were slightly greater in cannabis users compared to nonusers (odds ratio [OR]=1.31, 95% CI 1.13-1.51) (Warshak et al.). Greater odds of admission to the neonatal intensive care unit (NICU) were associated with cannabis use (OR=1.54, 95% CI 1.14-2.07) (Warshak et al.). In this retrospective cohort study of nearly 6,500 pregnant women with nearly 7,000 singleton births in Cincinnati, Ohio from 2008 to 2011, cannabis and tobacco co-use and cannabis-only use did not confer additional risks for adverse birth outcomes beyond tobacco-only use (Warshak et al.). Cannabis smoking was associated with increased odds of smaller head circumference (adjusted OR=2.34, 95% CI 1.27-4.31), a decrease in birthweight (BW) (adjusted OR=2.79, 95% CI 1.55-5.04), and preterm birth (PTB) (adjusted OR=2.56, 95% CI 1.33-4.94) (Chabarria et al.). Chabarria et al. (2016) used a retrospective cohort design to study approximately 12,000 pregnant women who delivered single births from 2011 to 2015 and compared outcomes in babies born to women who used cannabis alone during pregnancy, tobacco alone, and cannabis and tobacco concurrently.

Crume et al. (2018) found that there were increased odds of having a baby with LBW (OR=1.50, 95% CI 1.1-2.1) in prenatal cannabis users; there were no other significant differences in birth outcomes by cannabis use after controlling for tobacco use. Likewise, in nearly 4,000 singleton births in Connecticut from 1980-1982, babies born to mothers who used cannabis during pregnancy were 2.6 times more likely to be born at LBW in an adjusted model (95% CI 1.1-6.2), compared to mothers who did not use cannabis during pregnancy. They were also 2.3 times more

likely to be SGA (adjusted model, 95% CI 1.3-4.1). Current cigarette smoking may be a confounder for cannabis use; women who smoked cigarettes were over 3 times as likely to also use cannabis during pregnancy (OR=3.33, 95% CI 1.89-5.86). In an unadjusted univariate model, prevalence of VLBW was associated with cannabis use (10.0%) compared to no cannabis use (1.8%, p=0.032); however, this relationship disappeared when adjusting for tobacco use. Babies of cannabis users assessed retrospectively in Washington State between 2011 and 2016 were 1.42 times more likely to be born LBW (95% CI 1.01-2.01) and 1.51 times more likely to be SGA, adjusting for tobacco use (Straub et al.). Metz et al. (2017) looked at 1,610 liveborn neonates, enrolled prospectively in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Stillbirth Collaborative Research Network.

Cannabis use was associated with increased odds of composite neonatal morbidity (outcomes: spontaneous preterm birth, hypertensive disorders, and small for gestational age) or death, adjusting for tobacco & other illicit drug use and race (adjusted OR=3.11, 95% CI 1.40-6.91) (Metz, Allshouse, et al.). There were no other observed associations between cannabis use and adverse the pregnancy outcomes stated above (Metz, Allshouse, et al.). In Day et al.'s study of over 1,000 pregnant women (1991), birthweight increased in third trimester users compared to nonusers (3357.0 grams vs. 3215.0 grams, respectively), and birth length was shorter in first trimester users compared to nonusers (48.9 cm vs. 49.4 cm, respectively). Ko et al. (2018) looked at cross-sectional PRAMS data from Alaska, Hawaii, or Vermont between 2009 and 2011 and did not find any differences in birth outcomes between those who used cannabis during pregnancy and those who did not, controlling for cigarette use. Coleman-Cowger, Oga, et al. (2018) studied 500 pregnant women in Maryland in 2017. Cannabis use was associated with increased odds of decreased head circumference (adjusted OR=5.7, 95% CI 1.1-28.9) and of a birth defect (adjusted

OR=3.1, 95% CI 1.2-8.3) in cannabis and tobacco co-users compared to non-users (Coleman-Cowger, Oga, et al.). In women who only used cannabis, use was associated with increased odds of decreased head circumference, though the effect size was not as large (adjusted OR=3.0, 95% CI 1.1-9.1). Among those who only used cannabis, use was not associated with increased odds of birth defects (adjusted OR=1.2, 95% CI 0.5-2.9). The effect size also smaller in this relationship. These results suggest that cannabis and cannabis & tobacco co-use have differential effects on neonatal outcomes; co-use appears to be associated with greater odds of detrimental outcomes.

Table 6 is a compilation of various adverse birth outcomes, including the strength of association between prenatal use and the specific outcome, the statistical significance, and a summary of the direction of the association. A positive association between prenatal cannabis use and birth outcomes indicates that prenatal use was associated with improved outcomes. A negative association indicates that prenatal used was associated with detrimental outcomes (ex: a decrease in birthweight). A null association indicates that the observed association did not reach statistical significance. Nine unique studies observed null findings (Coleman-Cowger, Oga, et al.); (Conner et al.); (Ko, Tong, et al.); (Linn et al.); (Day et al.); (Crume et al.); (Gnofam et al.); (Chabarria et al.); (Metz, Allshouse, et al.) or a positive association (Day et al.) between cannabis use and birth outcomes. Ten unique studies found a negative association between prenatal use and neonatal outcomes (Coleman-Cowger, Oga, et al.); (Chabarria et al.); (Crume et al.); (Hatch and Bracken); (Howard et al.); (Mark, Desai and Terplan); (Straub et al.); (Metz, Allshouse, et al.); (Gnofam et al.); (Warshak et al.). Whether the study additionally controlled for prenatal tobacco use was included, as prenatal tobacco and cannabis use are important correlates.

Two studies assessed the relationship between prenatal cannabis use and APGAR score (Coleman-Cowger, Oga, et al.); (Conner et al.), one assessed birth defects (Coleman-Cowger, Oga,

et al.), ten assessed birthweight (Chabarria et al.); (Conner et al.); (Crume et al.); (Day et al.); (Hatch and Bracken); (Howard et al.); (Ko, Tong, et al.); (Linn et al.); (Mark, Desai and Terplan); (Straub et al.), two assessed neonatal morbidity (Conner et al.); (Metz, Allshouse, et al.), one assessed fetal growth restriction (Gnofam et al.), three assessed head circumference (Chabarria et al.); (Coleman-Cowger, Oga, et al.); (Day et al.), five assessed NICU admission (Conner et al.); (Crume et al.); (Gnofam et al.); (Ko, Tong, et al.); (Warshak et al.), six assessed preterm birth (Chabarria et al.) (Crume et al.); (Gnofam et al.); (Ko, Tong, et al.); (Metz, Allshouse, et al.), and five assessed small for gestational age (Crume et al.); (Hatch and Bracken); (Metz, Allshouse, et al.); (Straub et al.); (Warshak et al.).

Table 6 Summary of Adverse Birth Outcomes Identified in Studies from the Literature Review

Birth Outcome, alphabetically	Findings	First author (year published), alphabetically within outcome	Association	Controlled for Pre-natal Tobacco Use
APGAR score	Adjusted OR=0.9 (95% CI 0.1-8.4)	Coleman-Cowger, Oga (2018)	Null	Yes
	Adjusted OR=1.2 (0.7-2.3)	Conner (2015)	Null	Yes
Birth defect	Adjusted OR=3.1, (1.2-8.3)	Coleman-Cowger, Oga (2018)	Negative	Yes
Birthweight (including LBW and VLBW)	↓ BW, adjusted OR=2.79 (1.55-5.04)	Chabarria (2016)	Negative	Yes
	LBW: adjusted OR=1.3 (0.91-1.8) (p=0.09)	Conner (2015)	Null	Yes
	LBW: adjusted OR=1.50 (1.1-2.1)	Crume (2018)	Negative	Yes
	↑ BW (3357.0 g in users vs. 3215.0 g in nonusers)	Day (1991)	Positive	Yes
	LBW: adjusted OR=2.6 (1.1-6.2)	Hatch (1986)	Negative	Yes
	↓ BW associated with positive screen initially and at delivery (2,925 grams) vs. negative screen (3,235 grams) (p<0.001)	Howard (2019)	Negative	Yes
	5.9% (4.8-7.2) in prenatal users vs. 5.3% (5.1-5.5) in nonusers (p>0.05)	Ko (2018)	Null	Yes
	LBW: adjusted OR=1.07 (0.87-1.31)	Linn (1983)	Null	Yes
	↑ VLBW assoc with cannabis use vs. no use (10% vs. 1.8%, p=0.032) in univariate analysis (not adjusted for tobacco use)	Mark (2016)	Negative	Yes
	LBW: OR=1.42 (1.01-2.01)	Straub (2019)	Negative	No
Composite neonatal morbidity	Adjusted OR=1.3 (0.96-1.6)	Conner (2015)	Null	Yes
	Adjusted OR=3.11 (1.40-6.91)	Metz (2017)	Negative	Yes
Fetal growth restriction	↑ FGR post-legalization in adjusted model, 5.1% vs. 2.9% (p=0.006)	Gnofam (2019)	Negative	Yes

Table 6 Continued

Head circumference	Adjusted OR=2.34 (1.27-4.31)	Chabarria (2016)	Negative	Yes
	Adjusted OR=5.7 (1.1-28.9)	Coleman-Cowger, Oga (2018)	Negative	Yes
	No difference in users (34.3 cm) vs. nonusers (34.2 cm) (p>0.05)	Day (1991)	Null	Yes
NICU admission	Adjusted OR 1.6 (0.7-3.5) (p=0.25)	Conner (2015)	Null	Yes
	Adjusted OR=1.0 (0.6-1.7) (p=1.0)	Crume (2018)	Null	Yes
	No diff post-legalization in adjusted model, 13.4% (after) vs. 15.0% (before) (p=0.263)	Gnofam (2019)	Null	Yes
	No diff in users (6.0% (4.6-7.9)) vs. nonusers (8.2% (7.5-8.9))	Ko (2018)	Null	Yes
	OR=1.54 (1.13-1.51)	Warshak (2015)	Negative	Yes
Preterm birth	Adjusted OR=2.56 (1.33-4.94)	Chabarria (2016)	Negative	Yes
	OR=1.3 (0.8-2.1) (p=0.20)	Crume (2018)	Null	Yes
	No diff post-legalization in adjusted model, 12.2% (after) vs. 12.6% (before) (p=0.802)	Gnofam (2019)	Null	Yes
	No difference in users (7.2% (5.1-9.9)) vs. nonusers (7.1 (6.5-7.6)) (p>0.05)	Ko (2018)	Null	Yes
	Adjusted OR=1.02 (0.82-1.27)	Linn (1983)	Null	Yes
	No difference in users (13.2%) vs. nonusers (6.2%) (p=0.08)	Metz (2017)	Null	Yes
Small for gestational age	Adjusted OR=1.3 (0.8-2.2) (p=0.30)	Crume (2018)	Null	Yes
	Adjusted OR=2.3 (1.3-4.1)	Hatch (1986)	Negative	Yes
	No diff in users (8.2%) vs. nonusers (7.4%) (p=0.83)	Metz (2017)	Null	Yes
	OR=1.51 (1.49-1.53)	Straub (2019)	Negative	No
	OR=1.31 (1.13-1.51)	Warshak (2015)	Negative	Yes

5.0 Discussion

5.1 Overview of Findings

State-specific policies on cannabis are constantly evolving. A majority of states now have medical and/or recreational cannabis programs, with most legislation for recreational programs passed within the past decade. In January 2020, a liberal recreational cannabis program will become effective in Illinois. As states continue to implement cannabis legislation and cannabis becomes even more accessible and its use more frequent by Americans across the country, it is necessary to consider the effects of cannabis on health. This essay sought to determine both the current state of cannabis use legality in the United States, as well as the relationship between prenatal cannabis use and birth outcomes. Twenty-one studies were included in the literature review; these studies provided a range of data on both prevalence of prenatal cannabis use and birth outcomes associated with prenatal use. Primarily, APGAR score, birth defect, birthweight, composite neonatal morbidity, fetal growth restriction, head circumference, NICU admission, preterm birth, and small for gestational age were studied as they pertain to prenatal cannabis use. Birthweight, NICU admission, preterm birth, and small for gestational age were the most common birth outcomes observed across the studies; however, evidence on their association with prenatal cannabis use was mixed. Section 5.2 below provides a critical review of the observed associations in the context of the specific studies conducted.

Some scholars posit that the time between legalization and a state's first cannabis sales may provide a natural cohort, through which to study changes in prevalence, reporting of cannabis use, neonatal outcomes, etc. (Straub et al.). A total of 13 states were specifically studied in the

articles retrieved for the literature review, not considering studies which assessed prevalence of cannabis use and/or birth outcomes at the national level. To note, six states (Alaska, California, Colorado, Massachusetts, Vermont, and Washington State) have fully comprehensive (medical & recreational) cannabis programs; the remaining seven (Connecticut, Hawaii, Maryland, Missouri, Ohio, Pennsylvania, and Texas) have mixed legality. As is evident from the summary in Table 5, the estimated prevalence of prenatal cannabis use at the state-level widely varies. There is no clear trend as to whether prenatal cannabis use is consistently greater *or* lower post-legalization as compared to pre-legalization, likely because an increase in cannabis use will occur before legalization. Estimates of any prenatal usage range from as low as 0.88% (Chabarria et al.) up to 29.3% (Mark, Desai and Terplan).

It may be useful to look at each state's specific policies about cannabis in order to better understand prevalence of use and increases in use (i.e., surrounding legalization). For example, some states have stricter programs about the type of cannabis product that can be sold, the quantity of product any one individual is allowed to have at a given time, the approved routes of administration, and more. Perception of risk may be associated with the social desirability bias, where individuals are more reluctant to report cannabis use based on its social acceptance and legality. As discussed previously, prevalence of cannabis use and perception of harm associated with its use have an inverse association, especially over the past two decades.

This literature review identified some consistency in evidence for the association between prenatal cannabis use and adverse neonatal outcomes, though not all findings are statistically significant and/or the studies have significant limitations. Some studies were at the national level while others were state-specific, which creates complications for understanding the true effect of cannabis use on the fetus. For studies at the national level, it is imperative to consider specific

populations (i.e., women living in rural vs. urban areas) and their unique characteristics, which may contribute to differences in prevalence and birth outcomes across states.

5.2 Critical Review of Studies Examining the Association Between Prenatal Cannabis Use and Adverse Neonatal Outcomes

Among the studies included in the literature review which provided data on the association between prenatal cannabis use and neonatal outcomes, the outcomes most frequently studied were APGAR score, birth defect, birthweight, composite neonatal morbidity, fetal growth restriction, head circumference, NICU admission, preterm birth, and small for gestational age. To summarize key results from these studies, APGAR score, a measure of neonatal health, was not found to be associated with prenatal cannabis use. In a study of over 8,000 pregnant women appropriately powered to detect between-group differences, Conner et al. (2015) reported no differences in APGAR scores of exposed neonates. Results from the Conner study may not generalize to other populations because the study sample was predominantly low SES and African American. Additional studies on the association between prenatal cannabis use and APGAR score are needed to better understand if there is an effect, though available evidence suggests that there is not.

Several studies (N=9) looked at the relationship between prenatal cannabis use and birthweight (including low birthweight and very low birthweight). Most results suggest a statistically significant increase in the odds of low birthweight or very low birthweight associated with prenatal cannabis use, with similar effect sizes of ORs ranging from 1.3 to 2.8. Conner et al. (2015) did not observe a significant association (OR low birthweight=1.3, p=0.09). This may be due to use of self-report data which could have misclassified pregnant women by cannabis use

status and biased the results towards the null. Trained obstetric research nurses extracted patient data from medical histories and records. No additional information was given about how women self-reported use. Day et al. (1991) observed an increase in birthweight based on third trimester cannabis use. It is important to note that this study did not include heavy substance users, was conducted in the mid-1980s when cannabis use was illegal and prenatal use was less frequent, and cannabis was less potent and used differently than it is today. Perhaps there is a (significant) decrease in birthweight associated with prenatal cannabis use that can only be detected with a substantial dose and/or frequency of use, or at the current potency of THC.

Gnofam et al. (2019) observed an increase in the prevalence of fetal growth restriction post-legalization in Colorado. Colorado has a fully comprehensive cannabis program, so individuals can access it for both medical and recreational purposes. Post-legalization prevalence was 5.1% in an adjusted model, comparted to 2.9% pre-legalization (p=0.006). Though no other studies in this literature review of American studies provided data on fetal growth restriction as related to prenatal cannabis use, Generation R (GenR), a population-based prospective cohort in Rotterdam, Netherlands, has data on this relationship. Rotterdam is the second largest city in the Netherlands and is located in the western part of the country (Jaddoe et al.). Cannabis has long been legal in the Netherlands. GenR seeks to identify early environmental and genetic factors related to offspring growth, development, and health (Jaddoe et al.). Around 10,000 (n=9,778) women with a delivery date between April 2002 and January 2006 were enrolled; participants were followed from fetal life through adulthood (Jaddoe et al.). Enrollment was completed on a rolling basis, with 91% of women enrolled during pregnancy and 9% at birth (Jaddoe et al.). Fetal weight in offspring exposed to cannabis had a growth reduction of 14.44 grams per week (95% CI 5.94-22.94) compared to those not exposed to cannabis (p=0.001) (El Marroun, Hudziak, et al.).

An increase in the odds of smaller head circumference associated with prenatal cannabis use was found in Chabarria et al. (2016) and Coleman-Cowger, Oga, et al. (2018), with adjusted odds ratios of 2.34 (1.27-4.31) and 5.7 (1.1-28.9), respectively. A large sample size (Chabarria et al.); (Coleman-Cowger, Oga, et al.), using both electronic medical record and patient query – though not by the patient's healthcare provider – to assess prenatal cannabis use (Chabarria et al.), and/or using hair and urine samples in addition to electronic medical record review (Coleman-Cowger, Oga, et al.) provide strength for this association. However, the studies were not longitudinal and Coleman-Cowger, Oga, et al. (2018) did not capture information on dose, timing, and mode of cannabis consumption, therefore limiting the available evidence on the relationship between head circumference and prenatal cannabis use, especially because Day et al. (1991) found no difference in head circumference between users and nonusers. In GenR, fetuses with cannabis exposure had a smaller head circumference of 0.21 mm per week (95% CI 0.02-0.42) compared to those without cannabis exposure (p=0.07) (El Marroun, Tiemeier, Steegers, et al.).

Available evidence suggests that there may not be a detrimental impact of cannabis use on preterm birth, after adjusting for prenatal tobacco exposure that commonly occurs with prenatal cannabis exposure. Only Chabarria et al. (2016) observed increased odds of preterm birth in cannabis users compared to nonusers (adjusted OR=2.56, 95% CI 1.33-4.94). Crume et al. (2018), Gnofam et al. (2019), Ko et al. (2018), and Metz et al. (2018) found no statistically significant differences in either odds or prevalence of preterm birth in cannabis users. Gnofam et al. (2019) specifically studied changes in cannabis use over the legalization period in Colorado. Pre-legalization prevalence of preterm birth was 12.6%, compared to a post-legalization prevalence of 12.2% (p=0.802). This was one of the first studies to assess how legalization is associated with prenatal cannabis use. However, it is limited because it did not adjust for relevant confounders and

only included a single tertiary healthcare center in the state, so there was no comparison group. Given these mixed findings, future research should assess the relationship between prenatal cannabis use and preterm birth.

Other studies which have provided information on the relationship between prenatal cannabis exposure and neonatal outcomes are the Maternal Health Practices and Child Development Study and the Ottawa Prenatal Prospective Study. Based in the United States, Maternal Health Practices and Child Development study (MHPCD) studied women and their offspring in Pittsburgh, Pennsylvania. Briefly, the project is a longitudinal study on the long-term effects of prenatal cannabis or alcohol exposure on offspring. Women ≥18 years were recruited from a prenatal clinic and subsequently selected to participate in one or more cohorts studying 1) "all women who used marijuana at least twice a month in the first trimester, and the next woman interviewed who used less than that amount or none" and 2) "all women who drank three or more drinks a week, and the next woman interviewed who used less than that amount or none" (Day, Leech and Goldschmidt). The study sample was primarily low-SES (Day et al.). Data collection took place between 1983 and 1986 (Day et al.). Women were interviewed during pregnancy, at delivery, and at several times following birth; offspring were also assessed at the same timepoints (Day, Leech and Goldschmidt). In a paper included in this review which studied prenatal cannabis exposure and neonatal outcomes using MHCPD data, authors reported no association between prenatal cannabis use and offspring birthweight, head or chest circumference, or morphological development (Day et al.). Additionally, the Ottawa Prenatal Prospective Study (OPPS), conducted in the 1970s in Ottawa, Canada was not included in the review because it took place outside of the United States. OPPS enrolled a primarily white, middle-class, low-risk pregnant, most often early during the gestational period, starting in 1978, to study maternal lifestyle habits (Fried "The Ottawa

Prenatal Prospective Study (Opps): Methodological Issues and Findings--It's Easy to Throw the Baby out with the Bath Water"). Women and their offspring were assessed during fetal life and at least annually until offspring reached age 6, after which assessments were less frequent (Fried "The Ottawa Prenatal Prospective Study (Opps): Methodological Issues and Findings--It's Easy to Throw the Baby out with the Bath Water"). Women provided self-report data on drug use, with multiple assessments over time which helped with test-retest reliability (Fried "The Ottawa Prenatal Prospective Study (Opps): Methodological Issues and Findings--It's Easy to Throw the Baby out with the Bath Water").

Fried and Day both advocated for long-term follow-up, especially because certain developmental dysfunctions may not be expressed until well after birth as neurocognitive systems continue to develop in childhood (Fried "Conceptual Issues in Behavioral Teratology and Their Application in Determining Long-Term Sequelae of Prenatal Marihuana Exposure"). Also, more effects were detected long-term in both of these cohorts (Fried "Conceptual Issues in Behavioral Teratology and Their Application in Determining Long-Term Sequelae of Prenatal Marihuana Exposure"). Particularly, executive functioning – a “top-down” cognitive construct – continues to evolve with age and does not fully mature until puberty/early adulthood (Fried "Conceptual Issues in Behavioral Teratology and Their Application in Determining Long-Term Sequelae of Prenatal Marihuana Exposure"). Additionally, the external, postnatal environment becomes increasingly important for a child’s functions as s/he ages (Fried "Conceptual Issues in Behavioral Teratology and Their Application in Determining Long-Term Sequelae of Prenatal Marihuana Exposure"). Similarly, it has been suggested that in-utero drug exposure may have a transient/temporary effect on neonates, which may explain the lack of significant differences between exposure groups over time (Fried "Conceptual Issues in Behavioral Teratology and Their Application in Determining

Long-Term Sequelae of Prenatal Marihuana Exposure"). Thus, studying prenatal cannabis exposure presents unique challenges, and results must always be interpreted in light of the specific population and time period (especially developmentally) during which data were collected. The THC concentration in cannabis products has increased over the past several decades; since OPPS was conducted approximately 40 years ago, the THC concentration is likely much lower and may explain the observed findings (Fried "The Ottawa Prenatal Prospective Study (Opps): Methodological Issues and Findings--It's Easy to Throw the Baby out with the Bath Water"). Understanding the methodology and findings from studies such as GenR, MHPCD, and OPPS helps to provide a more comprehensive understanding of the association between prenatal cannabis use and neonatal outcomes. These studies also demonstrate the importance of long-term, longitudinal research on the effects of prenatal cannabis exposure on birth outcomes.

5.3 Strengths

5.3.1 Strengths of Literature Review

This paper uniquely and simultaneously investigates the prevalence of prenatal cannabis use as well as the association of prenatal cannabis use with adverse birth outcomes. Given recent evidence that suggests an increase in the prevalence of prenatal cannabis use over the past few decades, coupled with a decrease in the perception of risk associated with cannabis use (Substance Abuse and Mental Health Services Administration "Key Substance Use and Mental Health Indicators in the United States: Results from the 2018 National Survey on Drug Use and Health") and an increase in cannabis legalization, both medicinally and recreationally (DISA Global

Solutions); (National Conference of State Legislatures), it is of public health importance to better understand cannabis use in a pregnant population and its implications for neonates.

Though the geographic region was restricted to the United States only, the studies identified in the literature review covered a number of states (Alaska, California, Colorado, Connecticut, Hawaii, Maryland, Massachusetts, Missouri, Ohio, Pennsylvania, Texas, Vermont, and Washington State) as well as several studies at a multistate or national level. Furthermore, a few of these studies focused on cannabis use associated with recreational and/or medicinal cannabis legalization at the state-level (Crume et al.); (Gnofam et al.); (Straub et al.); (Metz, Silver, et al.), which provided insights on changes in patterns of use over time. No time frame was identified (i.e., studies reviewed took place at any point in time), which provided an organic perspective of cannabis use over time. Studies were published as early as the 1980s and as recently as 2019, reflecting temporal trends in the association between cannabis use in pregnancy and birth outcomes.

5.3.2 Strengths of Cannabis Research

Several studies specifically looked at concurrent tobacco and cannabis use and/or controlled for maternal tobacco co-use (Warshak et al.); (Linn et al.); (Howard et al.); (Crume et al.); (Coleman-Cowger, Pickworth, et al.); (Hatch and Bracken); (Chabarria et al.); (Mark, Desai and Terplan); (Ko, Tong, et al.); (Conner et al.); (Day et al.); (Coleman-Cowger, Oga, et al.); (Gnofam et al.); (Metz, Allshouse, et al.). As cannabis and tobacco are both widely used during pregnancy, it is important to consider their simultaneous use, as understanding trends in prenatal tobacco use may help explain trends in prenatal cannabis use, and vice-versa. Additionally, if a large proportion of women who use cannabis during pregnancy also use tobacco, and given the

evidence that prenatal tobacco exposure predicts adverse birth outcomes (Cornelius and Day), capturing prenatal tobacco use is necessary to understand whether adverse birth outcomes can be attributed to the effect(s) of prenatal cannabis exposure.

Sample size and representativeness of the study sample provided strength of evidence for many studies. Several studies reviewed had a substantial sample size (Warshak et al.); (Alshaarawy and Anthony); (Crume et al.); (Chabarria et al.); (Ko, Tong, et al.); (Straub et al.); (Conner et al.); (Metz, Allshouse, et al.); (Coleman-Cowger, Oga, et al.); (Ko, Farr, et al.); (Young-Wolff, Sarovar, Tucker, Conway, et al.) Furthermore, Alshaarawy & Anthony (2019) and Ko, Farr, et al. (2015) had a nationally representative sample of prenatal cannabis users. In a pooled analysis of 2002-2017 NSDUH data, pregnant users were more likely to be dependent on cannabis compared to nonpregnant users (adjusted OR=1.37, 95% CI. 1.07-1.77) and the prevalence of cannabis dependence was greater among pregnant users versus nonpregnant users (19.2% vs. 12.7%) (Alshaarawy and Anthony). Using 2007-2012 NSDUH data, authors found that 10.9% of pregnant women reported past-year cannabis use, with 3.9% reporting past-month use, compared to 14.0% of nonpregnant women reporting past-year use and 7.6% reporting past-month use (Ko, Farr, et al.).

Four studies employed multiple methods of detecting and assessing prenatal cannabis, such as self-report and urine toxicology screening (Warshak et al.); (Mark, Desai and Terplan); (Chang et al.) and urine toxicology screening and hair sample collection (Coleman-Cowger, Oga, et al.). Finally, capturing multiple years of repeated (cross-sectional) data enhanced the validity of the studies' reported findings (Roberson, Patrick and Hurwitz); (Ko, Farr, et al.); (Ko, Tong, et al.); (Coleman-Cowger, Pickworth, et al.); (Alshaarawy and Anthony); (Straub et al.); (Young-Wolff, Sarovar, Tucker, Conway, et al.). Longitudinal assessments allow researchers to capture changes

in trends, or lack thereof, over time, facilitating a better understanding of the epidemiology of cannabis use. Some studies looked specifically at pre- and post-legalization changes. For example, Gnofam et al. (2019) assessed prenatal cannabis use before, during, and after the commencement of Colorado's first recreational cannabis sales on January 1, 2014. The estimated prevalence of cannabis use, collected by self-report or through bio-detection, was 3.7% in 2012, 4.7% in 2013, 8.6% in 2014, and 5.9% in 2015 (p=0.02) (Gnofam et al.). Results from this study suggest that prenatal cannabis use was greatest in the year immediately after recreational sales began, and though it dropped in the next year, overall prevalence still remained greater than it was pre-legalization. With a greater prevalence of cannabis use associated with legalization, studies which incorporated cannabis legalization may have a more comprehensive understanding of adverse birth outcomes associated with prenatal cannabis use.

5.4 Limitations

5.4.1 Limitations of Literature Review

This research has limitations. It is possible that some titles and abstracts were excluded from and/or included in full text review that would not have been done if multiple scholars reviewed the titles and abstracts together. Only one database, PubMed, was used for the literature review. Additionally, only studies that focused primarily on cannabis use were evaluated. It was difficult to determine the sole prevalence of prenatal cannabis use and its association with adverse birth outcomes in studies that looked at polysubstance use. Birth outcomes were only considered/assessed immediately after birth; studies that focused on long-term offspring outcomes

were excluded from review. However, perhaps there were more significant and clinically relevant outcomes that occurred months or even years after birth; thus, a key limitation of this research was not identifying the full possible scope of associations between prenatal cannabis use and effects to the offspring.

5.4.2 Limitations of Cannabis Research

Furthermore, there are important limitations of available cannabis research to address. Primarily, study design greatly contributes to the quality and strength of evidence available. Because cross-sectional studies capture both exposure and outcome at a single point in time, they do not provide the strength of evidence necessary to demonstrate causality. Additionally, they do not allow for longitudinal collection of data on cannabis use, such as frequency and dose, over time. Experimental study designs, such as randomized controlled trials (RCTs), provide greater strength of evidence. However, in a pregnant population, it is neither ethical nor feasible to conduct an RCT, even as cannabis policies continue to change and recreational legalization at the state-level is more common. As discussed in a previous section, funding and other opportunities to conduct cannabis health research are limited, due to both structural barriers (National Academy of Sciences) and the federal government's regulation of cannabis as a Schedule I substance (United States Drug Enforcement Administration). Furthermore, there is support for a dose-dependent relationship between cannabis and its impact on the body (Spindle et al.). Studies which do not collect information on the timing of exposure (e.g., trimesters), amount of product, cannabinoid ratio (CBD:THC), quantity and frequency of use, and route of administration for an individual user may not accurately capture the true impact of cannabis on the body, as well as nuances associated with different patterns of use (ex: chronic vs. infrequent user).

Specific to the population of interest for this literature review, pregnant women, there may be misclassification or missing information associated with the timing of cannabis use. For example, women who reported past-year cannabis use around the time of pregnancy may not have actually used cannabis during their pregnancy, as a normal gestation is nine months. Therefore, it may appear as though some women used cannabis during pregnancy when in reality they did not, inflating the observed association away from the null. The method of data collection is also important to consider. Several studies (Linn et al.); (Alshaarawy and Anthony); (Coleman-Cowger, Pickworth, et al.); (Chang et al.); (Metz, Silver, et al.); (Ko, Farr, et al.); (Young-Wolff, Sarovar, Tucker, Conway, et al.); (Crume et al.); (Hatch and Bracken); (Gnofam et al.); (Roberson, Patrick and Hurwitz); (Mark, Desai and Terplan); (Ko, Tong, et al.); (Conner et al.); (Metz, Allshouse, et al.); (Day et al.); (Metz, Allshouse, et al.) relied on self-report data. All methods of data collection have their respective strengths and limitations. Various articles have discussed the differences, benefits, and drawbacks from different methods of ascertaining prenatal cannabis use, including El Marroun et al. (2011), Day, Cottreau, and Richardson (1993), and Richardson, Huestis, and Day (2006).

In the GenR study, which took place in the Netherlands where cannabis is legal, both self-report data and urine samples were collected from pregnant women (El Marroun, Tiemeier, Jaddoe, et al.). When compared to each other, self-report and urinalysis showed substantial specificity but moderate sensitivity, indicating that women who do not self-report cannabis use during pregnancy are likely not to have a positive screen (El Marroun, Tiemeier, Jaddoe, et al.) Self-report data may lead to misclassification of prenatal cannabis use, if women are reluctant to report using an illicit substance in general, especially during pregnancy. However, recent changes in legalization may have increased societal acceptance of cannabis use, so individuals may be more

forthcoming to self-report cannabis use. Recall and/or reporting bias may be related to societal acceptance and cannabis' legality (El Marroun, Tiemeier, Jaddoe, et al.). Self-report data is noninvasive and allows for substantial detail, which helps researchers to determine if there are trimester-specific effects on development (Richardson, Huestis and Day). Yet, they are susceptible to recall and other biases such as the social desirability bias (Day, Cottreau and Richardson). The nature and characteristics of the interviewer are also important; for example, participants are more inclined to disclose information to someone who does not provide medical care to them (Richardson, Huestis and Day).

On the other hand, biological samples such as urine, hair, and blood have varying windows of detection and do not provide details such as frequency and timing of use, as well as product used and patterns of use (Day, Cottreau and Richardson). Urine tests typically only capture recent use (within a few days), except in heavy users (Richardson, Huestis and Day). Furthermore, individuals who provide urine samples – in this context, pregnant women – because they sought care or treatment in a clinical setting may differ from those who are not seen in a clinical setting, therefore not accurately capturing true trends or patterns in use among the general population (Richardson, Huestis and Day). However, urine tests are advantageous because they are reliable, less costly, and easily available in a clinical and laboratory setting (Richardson, Huestis and Day). Therefore, the method(s) used to determine prenatal cannabis use must be considered when interpreting the results from a study.

As is with all epidemiological research, an ancillary but important limitation is the publication bias. Because research that shows statistically significant results tends to be published more often than does research with null findings, it is possible that clinically relevant findings were observed but simply not published (Dwan et al.). This limits the scope of literature available

and prohibits scholars from being able to make truly definitive conclusions about a given association; in this case, the association between prenatal cannabis use and adverse neonatal outcomes.

5.5 Conclusions and Future Directions

An interesting area of future research could be to study states which initially had medical cannabis programs and (recently) switched to comprehensive medical + recreational cannabis programs. Because there is no federal regulation for cannabis beyond its classification as a Schedule I substance, the burden falls on states to put in place a regulatory framework for cannabis (Tilburg, Hodge and Gourdet). Perhaps differences in prevalence may be seen in the type of cannabis program that is allowed under each state's law, so studying the specific program and legislation in place may lead to more insights about prenatal cannabis use. Furthermore, each state with a medical cannabis program has a list of qualifying conditions for which cannabis may be recommended therapeutically. The specific conditions may also be associated with certain users. Thus, it is wise to understand what types of individuals, including pregnant women, may seek medical cannabis. Finally, THC levels in cannabis products have changed over time, with a trend towards increasing potency (El Marroun, Tiemeier, Steegers, et al.); (Fried "The Ottawa Prenatal Prospective Study (Opps): Methodological Issues and Findings--It's Easy to Throw the Baby out with the Bath Water"). The prevalence of prenatal cannabis use, as well as the association between prenatal use and birth outcomes, may therefore reflect a change in the potency of THC rather than simply changes in cannabis use.

Public health surveillance and research efforts should continue to focus on assessing and understanding prenatal cannabis use and its association with adverse birth outcomes, especially in the context of rapidly evolving policies which increasingly favor cannabis' legalization.

Appendix A Glossary

APGAR: Appearance, Pulse, Grimace, Activity, and Respiration. A method using a scoring system to rapidly assess status immediately after birth and determine the need for interventions to establish breathing (https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/The-Apgar-Score?IsMobileSet=false)
BW: Birthweight. Usually measured in grams.
CI: Confidence interval.
FGR: Fetal growth restriction. Describes neonates smaller than expected given the number of weeks of pregnancy, with a birthweight below the 10th percentile. Also known as small for gestational age. (https://www.stanfordchildrens.org/en/topic/default?id=intrauterine-growth-restriction-iugr-90-P02462)
LBW: Low birthweight. Weight <2,500 grams. (https://www.who.int/whosis/whostat2006NewbornsLowBirthWeight.pdf)
LOS: Length of stay during a single hospital admission.
NAS: Neonatal Abstinence Syndrome. Conditions caused by a neonate's withdrawal from drugs exposed to in-utero. (https://www.marchofdimes.org/complications/neonatal-abstinence-syndrome-(nas).aspx)
NICU: Neonatal Intensive Care Unit.
NSDUH: National Survey on Drug Use and Health.
OR: Odds ratio. A measure of the strength of association between 2 events.
PRAMS: Pregnancy Risk Assessment Monitoring System. CDC and state health department collaborative surveillance project to collect "state-specific, population-based data on maternal attitudes and experiences before, during, and shortly after pregnancy." (https://www.cdc.gov/prams/index.htm)
PTB: Preterm birth. Birth before 37 weeks of completed gestation. (https://www.who.int/news-room/fact-sheets/detail/preterm-birth)
SGA: Small for gestational age. Describes neonates smaller than expected given the number of weeks of pregnancy, with a birthweight below the 10th percentile. (https://www.stanfordchildrens.org/en/topic/default?id=small-for-gestational-age-90-P02411)
SR: Self-report.
THC-A: Tetrahydrocannabinolic acid.
UDS: Urine drug screen.
VLBW: Very low birthweight. Weight <1,500 grams. (https://www.who.int/whosis/whostat2006NewbornsLowBirthWeight.pdf)

Appendix B State Cannabis Laws

Appendix Table 1 State Cannabis Laws (Medical and/or Recreational) by Year

State, alphabetically	Legal Status	Law	Year of Law (chronological within state)	Medical	Decriminalized
Alabama	Fully Illegal	SB 174	2014	No	No
		HB 61	2016		
Alaska	Fully Legal	Measure 8	1998	Yes	Yes
		Statute 17, Chapter 37	1998		
		SB 94	1999		
Arizona	Mixed	Proposition 203	2010	Yes	No
Arkansas	Mixed	Issue 6	2016	Yes	No
California	Fully Legal	Proposition 215	1996	Yes	Yes
		SB 420	2003		
Colorado	Fully Legal	Amendment 20	2000	Yes	Yes
Connecticut	Mixed	HB 5389	2012	Yes	Reduced
Delaware	Mixed	SB 17	2011	Yes	Reduced
District of Columbia	Fully Legal	Initiative 59	1998	Yes	Yes
		L18-0210	2010		
Florida	Mixed	Amendment 2	2016	Yes	No
Georgia	Mixed	HB 1	2015	CBD Oil	No
Hawaii	Mixed	SB 862	2000	Yes	Reduced*
Idaho	Fully Illegal	SB 1146	Vetoed 2015	No	No
Illinois	Fully Legal*	HB 1	2013	Yes	Yes*
		SB 0007	2019 (effective 2020)		
Indiana	Mixed	HB 1148	2017	CBD Oil	No

Appendix Table 1 Continued

Iowa	Mixed	SF 2360, Medical Cannabidiol Act of 2014	2014; repealed in 2017, then replaced	CBD Oil	No
		HF 524, now Section 124E	2017		
Kansas	Fully Illegal	--	--	No	No
Kentucky	Fully Illegal	SB 124	2014	No	No
Louisiana	Mixed	SB 271	2017	Yes	No
Maine	Fully Legal	Question 2	1999	Yes	Yes
		LD 611	2002		
		Question 5	2009		
		LD 1811	2010		
		LD 1296	2011		
Maryland	Mixed	HB 702	2003	Yes	Reduced
		SB 308	2011		
		HB 180/SB 580	2013		
		HB 1101 – Chapter 403	2013		
		SB 923	2014		
Massachusetts	Fully Legal	Question 3	2012	Yes	Yes
		Regulations	2013		
Michigan	Fully Legal	Proposal 1	2008	Yes	Yes
Minnesota	Mixed	SF 2471, Chapter 311	2014	Yes	Reduced
Mississippi	Fully Illegal	HB 1231	2014	No	Reduced
Missouri	Mixed	Amendment 2	2018	Yes	Reduced
Montana	Mixed	Initiative 148	2004	Yes	No
		SB 423	2011		
		Initiative 182	2016		
Nebraska	Fully Illegal	Limited trial program not open to public	--	No	Reduced
Nevada	Fully Legal	Question 9	2000	Yes	Yes
New Hampshire	Mixed	HB 573	2013	Yes	Reduced
New Jersey	Mixed	SB 119	2009	Yes	No
New Mexico	Mixed	SB 523	2007	Yes	Reduced
New York	Mixed	A6357	2014	Yes	Reduced
North Carolina	Fully Illegal	HB 1220	2014	No	Reduced
		HB 766	2015		
North Dakota	Mixed	Measure 5	2016	Yes	Reduced
Ohio	Mixed	HB 523	2016	Yes	Reduced

Appendix Table 1 Continued

Oklahoma	Mixed	SQ 788	2018 (not operational yet)	Yes	No
Oregon	Fully Legal	Oregon Medical Marijuana Act	1998	Yes	Yes
		SB 161	2007		
Pennsylvania	Mixed	SB 3	2016	Yes	No
Rhode Island	Mixed	SB 791	2007	Yes	Reduced
		SB 185	2009		
South Carolina	Fully Illegal	SB 1035	2014	No	No
South Dakota	Fully Illegal	Limited trial program not open to public	--	No	No
Tennessee	Fully Illegal	SB 2531	2014	No	No
Texas	Mixed	SB 339	2015	CBD Oil	No
		Texas Compassionate Use Act	2019		
		HB 3703	2019		
Utah	Mixed	Prop 2	2018	Yes	No
Vermont	Fully Legal	SB 76	2004	Yes	Yes
		SB 7	2007		
		SB 17	2011		
		H.511	2018		
Virginia	Mixed	HB 1445	2015	CBD Oil	No
Washington	Fully Legal	Initiative 692	1998	Yes	Yes
		SB 5798	2010		
		SB 5073	2011		
West Virginia	Mixed	SB 386	2017	Yes	No
Wisconsin	Fully Illegal	AB 726, Act 267	2013	No	No
Wyoming	Mixed	HB 32	2015	CBD Oil	No

Adapted from: http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx and https://disa.com/map-of-marijuana-legality-by-state.

Appendix C Federal vs. State Regulatory Approach for Medical Cannabis

Appendix Table 2 Federal vs. State Regulatory Approach for Medical Cannabis

Regulation	Federal	State (# of states to which regulation applies)
Drug efficacy	Animal & human clinical trials req'd for FDA approval	N/A
Drug indication	FDA approval; off-label use permitted	Qualified disease/symptom required to be eligible for medical cannabis (27 states)*
Drug safety	Animal toxicity testing; mandatory safety reporting to FDA during all phases of human testing and post-approval safety monitoring period	Product safety testing required for all medical cannabis products prior to sale (18)
Grounds for denying treatment	N/A	Explicitly authorize permit revocation (24)
Medical waste (unused)	Controlled Substances Act regulation of disposal of unused medication	Explicit waste protocols (21)
Patient discrimination protection	Americans with Disabilities Act prohibits discrimination based on physical impairment	Medical cannabis patients explicitly protected from discrimination (14)
Patient privacy	Health Insurance Portability and Accountability Act of 1996	Medical cannabis privacy protected to some degree
Product dispensary restrictions	Controlled Substances Act section which addresses supply chain, storage, & reporting purchases, sales	Number of dispensaries per state (18); dispensary location (21); allowable stock amount (11)
Product labeling	Adherence to FDA label requirements	Med cannabis product label explicitly regulated (23)
Product packaging	Adherence to FDA packaging regulations	Explicit package requirements and/or restrictions (21)
Product supply source	Controlled Substances Act outlines FDA secure supply chain regulations	Dispensary supply source regulated (25)
Restricted use locations	N/A	Medical cannabis use prohibited in specific locations/facilities/situations (26)
Site safety features	Controlled Substances Act section which addresses supply chain security	Explicit site structural requirements (24)

Federal vs. State Regulatory Approach for Medical Cannabis. Table adapted from (Klieger et al.). *As of February 1, 2017.

Appendix D Summary of Twenty-one Studies Included in Literature Review on the Association Between Prenatal Cannabis Use and Adverse Neonatal Outcomes

Appendix Table 3 Studies Identified from the Literature Review (chronologically; and alphabetically within same year)

First Author, Year Pub.	Analytic Sample & Participant Characteristics	Study Design	Exposure(s)	Outcome(s)	Relevant Findings
Linn et al., 1983	12,424 pregnant women (1,426 cannabis users and 11,178 nonusers); delivered at Boston Hospital for Women Division of the Brigham and Women's Children Hospital from 8/1977-3/1980; excluded if had drug abuse problem; interview women post-delivery and review physician notes	Retrospective cohort	Cannabis use during pregnancy; previous medical/obstetrical history	Information on current pregnancy & its outcome	7.1% use cannabis occasionally, 1.8% weekly, and 1.1% daily (90.0% no use); cannabis users younger, African American, less educated, unplanned pregnancy; ↑ prevalence of ≥1 major malformation in offspring of users (33.7% of users vs. 26.3% of nonusers)
Hatch & Bracken, 1986	3,857 live singleton births; participants delivered at in the New Haven, Connecticut area from 5/1980-3/1982, speak English, and not know about the study ahead of time; interview within first few weeks of prenatal visit and medical record review of birth outcomes	Prospective study	Cannabis use during pregnancy (grouped into never, occasional, regular); if positive, inquired about frequency	LBW, gestational age, preterm delivery	5.4% of pregnant women used regularly, 4.1% occasionally, and 90.5% never; users more likely to be younger, nonwhite, less educated, tobacco/alcohol/caffeine co-users; ↑ odds of LBW (adjusted OR=2.6, 95% CI 1.1-6.2) and SGA (adjusted OR=2.3, 1.3-4.1) in regular vs. never users
Day et al., 1991	564 pregnant women in Phase 1 and 519 in Phase 2; ≥18 years, in 4th month of pregnancy from 5/1983-1/1986	Prospective longitudinal study with stratified probability sampling	Cannabis use during pregnancy, as well as other drug/alcohol use	Length, head and chest circumference, APGAR scores, BW, leanness, gestational age, congenital abnormalities	Cannabis use ↓ over 1st trimester (24% to 12%), prevalence of use 7% during 2nd and 3rd trimesters; cannabis users African American, unmarried, lower income, and illicit drug users; ↓ length in months 1 &2 associated w/ cannabis use (average length 48.9 cm vs. 49.9 cm in trimester 3); ↑ BW in third trimester users vs. nonusers (3357.0 grams vs.

Appendix Table 3 Continued

					3215.0 grams); no other impacts on birth outcomes
Roberson et al., 2014	55,690 live births from 2009-2011; part of Hawaii PRAMS dataset; secondary analysis of HI PRAMS data	Cross-sectional	Cannabis use during pregnancy and immediately postpartum; nausea during pregnancy	When severe nausea during pregnancy was exposure, outcome was cannabis use during pregnancy and postpartum	Pre-pregnancy users were younger and less educated; users during pregnancy were lower income, white, and had 1-3 years of college education; 6.0% (95% CI 5.2-6.8) reported using during the month before pregnancy and 2.6% (2.2-3.2) during pregnancy; 21.2% (19.8-22.8) women reported severe nausea, of which 3.7% reported cannabis use during pregnancy (prevalence ratio=1.63, 95% CI 1.08-2.44)
Conner et al., 2015	8,138 pregnant women; live, singleton, term-length pregnancies, delivered at Washington University at Saint Louis Medical Center from 2004-2008	Retrospective cohort	Cannabis use during pregnancy, identified through self-report or UDS	Composite neonatal morbidity and individual neonatal morbidity component (LBW, NICU admission, APGAR, etc.)	8.4% used cannabis during pregnancy; users were more likely to be African American, younger, polysubstance users; no differences in outcomes in adjusted models
Ko et al., 2015	93,373 pregnant women; 18-44 years old with pregnancy status and complete information on recent cannabis use available from NSDUH data from 2007-2012; secondary data analysis of NSDUH data	Cross-sectional	Pregnancy status and trimester (if applicable); patterns of an attitudes towards cannabis use; other drug/alcohol use	If cannabis user, categorized as substance abuser or dependent	10.9% of pregnant women reported past-year cannabis use, 3.9% (95% CI 3.2-4.7) past-month, 7.0% (6.0-6.2) past 2-12 months; 14.0% of nonpregnant women reported past-year use, 7.6% (7.3-7.9) past-month, 6.4% (6.2-6.6) past 2-12 months; users were younger, unemployed, single, lower SES; pregnant users more likely to show abuse/dependence vs. nonpregnant users
Warshak et al., 2015	6,488 pregnant women (361 cannabis users and 6,107 non-users), representing 6,841 singleton births at University of Cincinnati Medical Center from 1/2008-1/2011; medical record review	Retrospective cohort	Cannabis use, reported during prenatal care/delivery *or* a positive tox screen for THC during pregnancy	Preterm delivery, FGR, major fetal abnormality, SGA, NICU admission	Cannabis users more likely to be younger and tobacco users; ↑ SGA rate associated w/ cannabis use (adjusted OR=1.31, 95% CI 1.13-1.51); ↑ NICU admission rate associated w/ cannabis use (adjusted OR=1.54, 1.14-2.07) in tobacco non-users; cannabis & tobacco co-and cannabis-only use didn't confer additional risks over tobacco-only use

Appendix Table 3 Continued

Chabarria et al., 2016	12,069 pregnant women; delivered singleton at tertiary referral hospital from 1/2011-6/2015, provided information about smoking; used patient-reported, interview, and electronic medical record data	Retrospective cohort	Ever and current cannabis use, grouped into four categories	Preterm birth, APGAR scores, BW, head circumference and head circumference below mean, FGR	0.88% reported prenatal cannabis use, of which 45% were tobacco co-users; cannabis smokers were younger, single, African American compared to nonsmokers; cannabis smoking associated with ↓ head circumference (adjusted OR=2.34, 95% CI 1.27-4.31), ↓ BW (adjusted OR=2.79, 1.55-5.04), and PTB (adjusted OR=2.56, 1.33-4.94); no other significant differences in adverse neonatal outcomes
Mark et al., 2016	396 pregnant women; delivered at university-affiliated clinic in urban areas in Maryland from 7/2009-6/2010; received prenatal care	Retrospective cohort	Self-report or urine tox screen of cannabis use at first OB visit; cannabis use throughout pregnancy (urine tox screen); healthcare utilization	LBW, gestational age	29.3% screened positive from either method, w/ 46.6% concordance btwn methods; cannabis users less educated, unemployed, tobacco co-users; current cigarette smoking confounder for cannabis use (OR=3.33, 95% CI 1.89-5.86); ↓ prevalence of use throughout pregnancy: 21.8% during trimester 1, 17.5% during trimester 2, 0% during trimester 3; ↑ VLBW associated with cannabis use vs. no use (10.0% vs. 1.8%, p=0.032) in univariate analysis only (not adjusted for tobacco use)
Chang et al., 2017	422 pregnant patients; ≥18 years, English-speaking, attending first OB visit at 5 outpatient prenatal clinics/practices in Pittsburgh from 2/2011-8/2014, provided urine sample	Cross-sectional	Perinatal illicit drug use; patient-doctor communication	Prevalence of prenatal cannabis use; agreement between UDS and self-report	29% disclosed ever use and 20% current use; 87% of those who self-reported use had a positive drug screen; 46% of those who had a positive drug screen did not self-report use; overall prevalence of cannabis use, regardless of detection method, was 25.4%

Appendix Table 3 Continued

Metz et al., 2017	1,610 liveborn controls (897 had umbilical cord tissue available); nonanomalous singleton live-birth delivered ≥24 weeks from 3/2006-9/2008; secondary analysis of Eunice Kennedy Shriver National Institute of Child Health and Human Development Stillbirth Collaborative Research Network data	Prospective enrollment	Cannabis use during pregnancy, measured by self-report or THC detection in umbilical cord	SGA, preterm birth, NICU admission	Cannabis use in 2.7% of births: 1.6% detected by self-report (SR) and 1.9% detected by cord homogenate with some overlap; negligible agreement btwn SR and biospecimen collection (kappa=0.0575, 95% CI 0.056-0.172); cannabis use associated with tobacco and illicit drug use, less education; cannabis use associated with ↑ odds of composite neonatal morbidity or death (OR=3.11, 95% CI 1.40-6.91), adjusting for tobacco and other illicit drug use & race; no association with adverse pregnancy outcomes
Coleman-Cowger, Oga, et al., 2018	500 pregnant women; ≥18 years, English-speaking, provided hair sample, singleton pregnancy from one of two obstetric clinics in Maryland from 1/2017-12/2017; secondary data analysis	Cross-sectional study; retrospective electronic medical record chart review	Cannabis and tobacco co-use during pregnancy	BW, length, head circumference, gestational age, APGAR scores, birth defects, NICU admission	Co-users and cannabis only users were African American, unemployed; co-users were single, reported past-month alcohol/drug use, didn't plan pregnancy; 12.1% reported past-month cannabis only, 7.8% tobacco only, 9.0% co-use, 71.1% none; pregnancy intention best predictor of co-users vs. nonusers (adjusted OR=0.2, 95% CI 0.1-0.6); ↑ odds of ↓ head circumference (adjusted OR=5.7, 1.1-28.9) and ↑ odds of birth defect (adjusted OR=3.1, 1.2-8.3) in co-users vs. non-users
Coleman-Cowger, Pickworth, et al., 2018	8,695 pregnant women and 162,451 pregnant women from 2006-2016; 18-44 years old; secondary analysis of NSDUH data	Cross-sectional	Pregnancy status, when applicable	Self-report cigarette, cigar, and blunt use by pregnancy trimester, as well as between pregnant and nonpregnant women	↓ cigar/cigarette use in pregnant women (17.6%, SE=2.0% vs. 10.1%, SE=1.4% in 2016) and ↑ cannabis use in nonpregnant women (3.1%, SE=0.2% in 2006 vs. 5.2%, SE=0.2% in 2016); nonpregnant women more likely to use, controlling for tobacco co-use; greatest use among pregnant women in first trimester (3.9% in first trimester vs. 0.6% in third trimester; $p<0.001$)

Appendix Table 3 Continued

Crume et al., 2018	3,207 births, representing 128,784 mothers; Colorado resident who gave birth in-state from 2014-2015, delivered <4 children, ≥15 years old; secondary analysis of state-specific Colorado PRAMS data	Cross-sectional study using a stratified random sample	Trimester-specific prenatal cannabis use	LBW, preterm birth, SGA	5.7% (95% CI 4.8-6.8) of women reported cannabis use at any point during pregnancy, 4.8% (4.0-5.9) during the first trimester, and 2.4% (1.8-3.1) during the third; those who used were younger, less educated, white non-Hispanic, single, and lower SES, tobacco co-users; ↑ odds of LBW (OR=1.50, 95% CI 1.1-2.1) and no statistically significant differences in other outcomes by cannabis use after controlling for tobacco use
Ko et al., 2018	9,013 live births to mothers who reported prenatal cannabis use; part of Alaska, Hawaii, or Vermont PRAMS dataset from 2009-2011; secondary analysis of state-specific PRAMS data	Cross-sectional	Cannabis use during pregnancy	BW, gestational age, NICU admission/LOS, 1-week neonate checkup	Prevalence by state: AK- 6.6%, VT- 5.5%, HI- 2.8%; cannabis users younger, non-Hispanic white, single, less educated, lower SES, other substance users; no significant differences in birth outcomes between users and nonusers, controlling for cigarette use
Alshaarawy & Anthony, 2019	381,199 women; 12-44 years old, non-institutionalized US residents from NSDUH data sets: 2002-2005, 2006-2009, 2010-2010, 2014-2017; secondary analysis of NSDUH data	Cross-sectional	NSDUH year	Recent cannabis use (w/in 30 days prior to interview); cannabis dependence, assessed by DSM-IV	↑ in cannabis use over time in pregnant women during first trimester only (5.6%→8.1% 2002-2017); overall 4.0% (95% CI 3.6-4.5) of pregnant women reported using cannabis in the past 30 days; ↑ prevalence (19.2%, 15.5-23.6 vs. 12.7%, 12.3-13.2) and odds (adjusted OR=1.37, 95% CI 1.07-1.77) of dependence seen in pregnant vs. nonpregnant cannabis users
Gnofam et al., 2019	2,392 pregnant women (1,165 pre- and 1,227 post-legalization); delivered between 2012 and 2015 (segregated into before and after 1/1/2014, commencement of first recreational sales) at tertiary center in Colorado, first birth only if ≥1 delivery	Retrospective cohort	Time, pre- and post-legalization status; other drugs, alcohol, and tobacco use	Cannabis use, from self-report or bio detection, pre- and post-recreational dispensary opening; FGR, preterm birth, SGA, congenital abnormalities, mortality	↑ combined prevalence over legalization period (3.7% in 2012, 4.7% in 2013, 8.6% in 2014, 5.9% in 2015, p=0.02) and ↑ odds of cannabis use after legalization (adjusted OR=1.8, 95% CI 1.2-2.5); ↑ in FGR post-legalization in adjusted model (5.1% vs. 2.9%, p=0.006; adjusted OR=1.9, 95% CI 1.3-3.1); no other differences in birth outcomes

Appendix Table 3 Continued

Howard et al., 2019	2,173 pregnant women; singleton births at a large academic tertiary referral center from 8/2013-12/2014	Retrospective medical record review	Cannabis use as assessed by UDS, during pregnancy and at delivery	Gestational age, BW, length, head circumference, APGAR score, NAS, mortality	348 participants tested positive at the initial screen, 27 upon delivery, and 115 at both initial screen and delivery; those who screened positive initially more likely to be younger; lower BW associated with positive screen initially and at delivery (2,925 grams) vs. negative screen (3,235 grams) ($p<0.001$); neonates born to women who tested (+) at delivery and at both screens shorter by median length of 1 cm than those born to women who tested (–)
Metz et al., 2019	116 pregnant women with self-report data linked to umbilical cord assay; live singleton pregnancy, ≥24 weeks' gestation; delivered at one of two urban Colorado medical centers during 11/2016, speak English or Spanish, spend >2 hours in labor/delivery unit (to have time to collect data)	Cross-sectional study performed at time of delivery admission	Cannabis use, measured by 1) self-report, 2) report to healthcare provider, and 3) umbilical cord test	THC-A in cord sample; prevalence of cannabis use	2.6% of women SR cannabis use to provider, with 6.0% past-month use; 7 women used within past 30 days; 22.4% THC-A>limit of detection; overall, cord assays estimate greater prevalence than SR but no substantial agreement btwn measures; women 22-25 ↑ likely to have THC-A>limit of detection vs. not (48.0% vs. 15.7%, $p<0.001$) and have Medicaid (80.8% vs. 54.5%, $p=0.016$)
Straub et al., 2019	5,543 pregnant women (1,610 in Wave 1, 1,511 in Wave 2, and 2,222 in Wave 3); delivered at Tacoma General Hospital or Good Samaritan Hospital from 3/2011-11/2012; 11/212-7/2014; or 7/2014-3/2016, by wave, urine drug screen results available	Retrospective	Cannabis use during pregnancy (any positive screen classified woman as user)	Gestational age, BW, LBW, SGA, and preterm birth	Similar prevalence of cannabis use across three cohorts (average 23.73%, $p=0.815$); cannabis users slightly older, polysubstance users, lower income; babies born to cannabis users ↑ odds LBW (OR=1.42, 95% CI 1.01-2.01) ↑ odds SGA ($OR_{gross}=1.51$, $OR_{cohort\ 1}=1.49$, $OR_{cohort\ 2}=1.53$, $OR_{cohort\ 3}=1.43$)
Young-Wolff et al., 2019	276,991 women representing 367,403 pregnancies from 1/2009-12/2017; part of Kaiser Permanente Northern California healthcare system, >11 years	Longitudinal evaluation of cross-sectional data	Year	Self-reported cannabis use before and during pregnancy (categorized into none, ≤monthly, weekly, daily)	Overall use 9.0% before and 2.5% during pregnancy; 96.0% of women who used during pregnancy also used before pregnancy; users were younger, African American, lower SES; 2009→2017: year before pregnancy, prevalence ↑ 6.8% →12.5% ($p<0.001$); use during pregnancy ↑ 2.07→3.38 ($p<0.001$) greatest ↑ in daily use during pregnancy, 1.95% →3.38% ($p<0.001$)

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