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Research Article

A Systematic Review of the Association Between Prenatal Cannabis Usage and the Impact on Behavior and Cognitive Skills in Children

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Abstract

Background: As cannabis legalization around the world continues to rise, the importance of understanding its impact on our population increases. A population of great concern is our obstetric population as the teratogenic effects of cannabis are not well recognized.

Methods: A systematic review was completed using several online databases including PubMed, Science Direct, and Google Scholar using the search terms "prenatal cannabis use", "cannabis and behavioral control", and "cannabis exposure". The inclusion criteria for articles used in the results section were primary or secondary sources published no later than 2011, and those written in the English language. Study designs included cross-sectional, cohort, and animal studies. Those that met the criteria were investigated for behavioral outcomes of prenatal cannabis exposure through a critical appraisal of evidence. Secondary outcomes such as mood disorders and other behavioral concerns were also documented.

Results: Seven studies were included in this review. Results indicated that children who were exposed to cannabis in the womb demonstrated direct effects on aggression, cognitive scores, and delinquency compared to those without exposure. Additionally, prenatal exposure was found to have various indirect effects on the risk of psychopathy, depression, IQ, and anxiety.

Conclusion: Current studies have established various direct and indirect long-term behavioral concerns with prenatal cannabis use. Future studies should include more recent data to inform future policies and interventions for women of reproductive age.

Keywords: *Cannabis; Delinquency; Aggression; Child Development; Prenatal Exposure; Tetrahydrocannabinol; Neurodevelopment*

Abbreviations

α7nACh: α7 Nicotinic Acetylcholine; ABCD study: Adolescent Brain and Cognitive Development; BPM: Brief Problem Monitor; CBCL: Child Behavior Checklist; CB1: Cannabinoid Type 1; CB2: Cannabinoid Type 2; CDI: Children›s Depression Inventory; CI: Confidence Interval; DIS-IV: Diagnostic Interview Schedule-IV; ECS: Endocannabinoid System; GD: Gestational Day; GABA: Gaba Amino Butyric Acid; HR: Heart Rate; IQ: Intelligent Quotient; KYNA: Kynurenic Acid; LBW: Low Birth Weight; MeSH: Medical Subject Headings; MHPCD: Maternal Health Practices and Child Development Study; NAc: Nucleus Accumbens; NCBI: National Center for Biotechnology Information; NMDA: N-Methyl-D-Aspartate; PLEs: Psychotic-Like Experiences; PFC: Prefrontal Cortex; RSA: Respiratory Sinus Arrhythmia; SGA: Small for Gestational

Age; SBIS: Stanford-Binet Intelligence Scale; SRD: Self-report Delinquency Scale; SNAP: Swanson, Nolan, and Pelham Questionnaire; THC: 9-tetrahydrocannabinol; TBC: Toddler Behavior Checklist; TRF: Teacher Report Form; WIAT: Wechsler Individual Achievement Test; WRAML: Wide Range Assessment of Memory and Learning

Introduction

The use of recreational cannabis has grown around the world as more countries choose to legalize or decriminalize its use. While there are many benefits to legalization, such as medicinal use, and positive criminal justice outcomes [1], there is growing concern about early exposure of our younger population. It is, therefore, imperative that we fully comprehend the impact of early cannabis exposure on our vulnerable groups such as infants during the gestational period and their pregnant mothers.

Delta 9-tetrahydrocannabinol (THC) is the main psychoactive component of cannabis responsible for the short-term and possible long-term effects of early exposure to cannabis [2]. In humans, subjective effects include feelings of euphoria, changes in perception, slowed psychomotor performance, and anxiety [3]. THC can produce these psychoactive effects through its connection with receptors in the endocannabinoid system (ECS). The ECS is a group of endogenous cannabinoid receptors located throughout the nervous system and is responsible for many neurodevelopmental processes. It consists of two G protein-coupled receptors, cannabinoid type 1 (CB1) and type 2 (CB2) receptors, endogenous ligands, and synthetic and degradative enzymes and transporters. The ECS itself is vulnerable to plastic changes suggesting the possibility that external alterations can have long-term effects on its neural functioning [4].

The cannabinoid receptors (CB1) play a role in excitatory and inhibitory control of neural systems and are seen in higher volumes during adolescence. Studies on cannabinoids have found that THC increases the activity of dopaminergic neurons in regions of the brain important for reinforcement effects, known as the mesolimbic dopamine system [1]. Hence, many aim to discover if exposure to THC during the prenatal period influences the neurochemical structure and cognitive or behavioral outcomes later in life. A consistent finding among many studies is that most psychoactive drugs, including THC, could alter the structure of neurons in the prefrontal cortex (PFC), and nucleus accumbens (NAc) [5]. The study by Wrege., *et al*. (2014) indicated that chronic cannabis users had a decrease in PFC activation. The PFC plays a key role in various behavioral characteristics including reward regulation and goal-directed behavior, and therefore reduction in the PFC can be correlated with various behavioral concerns, such as impulsivity [6]. Areas within the PFC mature throughout childhood leaving some developmental processes more vulnerable to change than others, depending on the age of drug use [7].

THC is known to cross the human placenta, allowing the drug to reach the fetus in utero [8]. It is also highly lipophilic which permits easy transmission into breast milk [9]. The knowledge of its transmissibility and the upward trend of cannabis use, specifically in the pregnant population increases the concern for fetal exposure and possible toxic effects.

In the US, prenatal cannabis use has increased from 3.4% in 2002 to 7.0% in 2016 [10], while data from a North American-wide survey demonstrated an increase in prenatal cannabis use of 62% from 2002 to 2014 [11], and by 170% from 2009 to 2016 [12]. Though this increased use of recreational cannabis may pose a significant risk for both the mother and child, these outcomes are not well understood. Studies currently available indicate mixed findings, creating an environment of uncertainty for mothers and may have fostered the misconception that cannabis use poses no serious risks during pregnancy. According to a recent study, the average predicted probability of no risk of prenatal cannabis use amongst pregnant women increased from 3.5% to 16.5% over 10 years [13].

The American College of Obstetrics and Gynecology has reported poorer fetal outcomes with prenatal cannabis use including fetal growth restrictions, preterm births, negative neurodevelopmental outcomes, and increased neonatal intensive care admissions [8]. Additional studies have also demonstrated that prenatal cannabis use leads to low birth weight and higher risks of neonatal intensive care admissions [14,15]. However, there is little literature available regarding its long-term effects on emotion control and behavior.

To date, there have been very few prospective longitudinal studies examining the outcomes of prenatal cannabis exposure on neurodevelopment and behavioral deficits. The data from these studies include cognitive and behavioral effects including attention deficits, impulsivity, delinquent behavior, and aggression [16-18].

Aim of the Study

This study aims to test the hypothesis that prenatal exposure to cannabis leads to long-term deficits in behavioral control.

Materials and Methods

Search strategy

Several databases were used to complete the search including Google Scholar, NCBI, and Science Direct, however, full-text articles were accessed exclusively through Pubmed. The article search was filtered by publications dated between 2011 and 2021, the type of study, and those that represented the analysis of this review. Articles were obtained using a combination of the key phrases: marijuana use, fetal drug exposure, maternal cannabis dependence, Prenatal marijuana exposure, cannabis AND impulse control, fetal outcomes, AND maternal cannabis use. Subsequent searches were carried out with 'impulse control', 'attention deficits', and 'behavioral outcomes' as MeSH terms for 'cannabis exposure'. A flow diagram (Figure 1) summarizes the process of article collection.

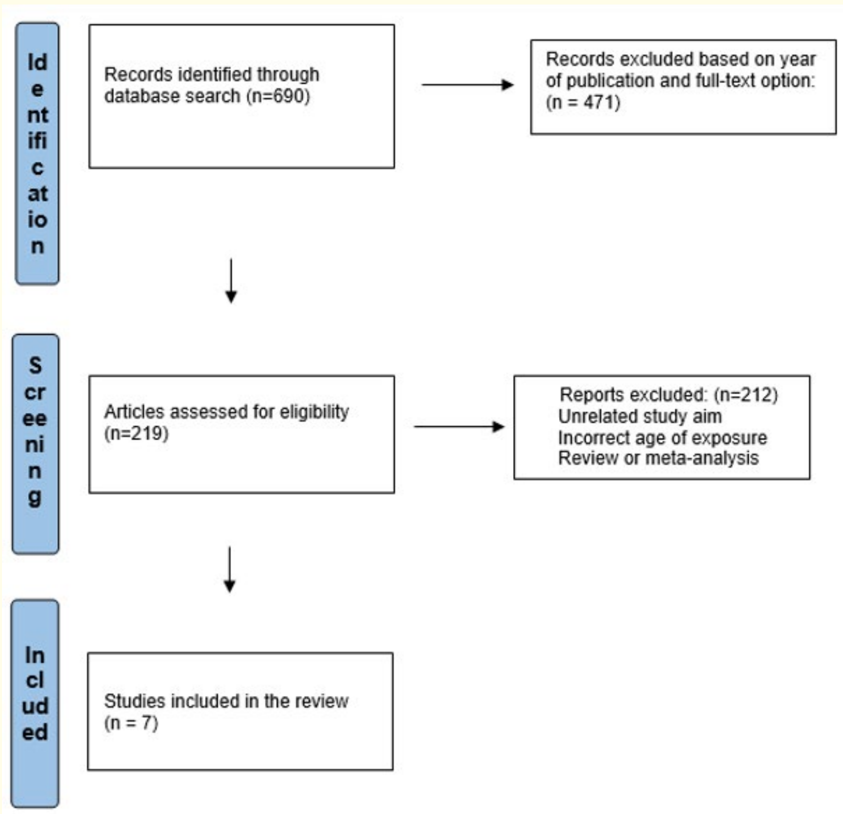

Figure 1: *PRISMA chart summarising the identification of study selection.*

Inclusion and exclusion criteria

Inclusion criteria included various studies of the pregnant population with a history or confirmed use of cannabis. The primary and secondary behavioral effects of cannabis on the child exposed in utero were the focus of research. The articles included were published in English, no earlier than 2011. The ranking of the journal of publication and citations were also taken into consideration while assessing the articles. Exclusion criteria included any systemic reviews, meta-analyses, or articles published before 2011. Any research focusing on adverse fetal outcomes immediately after birth was not included.

Data analysis

Articles that were independently reviewed to have met the criteria listed above, were compiled into an evidence table in 1. This search led to a total of 219 articles that met the selection criteria, from which only 7 were selected for final review.

Qualitative analysis

This systematic review is a qualitative analysis of prospective and observational studies. The study aims to investigate the long-term direct and indirect effects of prenatal exposure to cannabis. The direct effects include any significant drop in school grades and delinquent behavior. Indirect effects include secondary findings of depression, impulsivity, and attention deficits.

Results

Identified studies

After applying the inclusion and exclusion criteria, a total of seven peer-reviewed articles published between 2011 and 2021 were selected for the study. These included one animal study [19], four non-randomized control trials [20-23], and two observational studies [24,25]. Table 1 indicates the organization of these studies.

First Author	Date of Publication	Study Design	Level of Evidence	Study Population	Exposure	Outcome
Beggiato, S [19]	March 2017	Clinical Study-Animal	0	Wistar rats	Pregnant rats were exposed to cannabis during various gestational days.	Results showed that prenatal cannabis exposure led to an increased level of KYNA, and decreased glutamate in the PFC of those offspring. Imbalanced levels of KYNA and glutamate have been linked to various psychiatric diseases and aggression.
Day, N.L [22].	February 2011	Non-randomized controlled trial	2	763 children born to mothers with a positive history of cannabis use. Recruited from the MHPCD study.	Children in the exposed group were either exposed to cannabis or alcohol in utero.	Children with prenatal exposure were associated with higher rates of delinquency, depression, and attention.
Eiden, RD [23]	July 2018	Non-randomized controlled trial	2	247 mother-infant dyads	Children are exposed to tobacco, cannabis, or a combination of the two.	Results showed children exposed to cannabis in utero had a more difficult time regulating their emotions compared to the control.

El Marroun, H [24]	February 2019	Cohort	3	5903 children born to mothers with a positive history of cannabis use during pregnancy.	Children exposed to cannabis in utero.	Children with prenatal exposure were found to have greater difficulty with externalizing problems.
Goldschmidt, L [20]	June 2016	Non-randomized controlled trial	2	763 children born to mothers with a positive history of cannabis use. Recruited from the MHPCD study.	Children in the exposed group were either exposed to cannabis or alcohol in utero.	Children with prenatal exposure were associated with negative adult roles and difficult childhood behaviors.
Goldschmidt, L [21]	Jan 2012	Non-randomized controlled trial	2	763 children born to mothers with a positive history of cannabis use. Recruited from the MHPCD study.	Children in the exposed group were either exposed to cannabis or alcohol in utero.	Children with prenatal exposure were associated with poorer school achievement at age 14, mediated by a decrease in IQ, and increased risk of depression.
Paul, S [25]	September 2020	Cross-Sectional Study	3	655 children out of 11 489 who were recruited from the ABCD study.	Prenatal cannabis exposure before and after maternal knowledge of pregnancy.	Children with prenatal exposure were associated with an increase in psychopathy characteristics and greater difficulties with attention and externalizing issues.

Table 1: *Summary of studies reviewed.*

Sample population characteristics

The sample populations of the prospective and retrospective studies included pregnant females and their progeny from that pregnancy. Pregnant mothers were followed from the antenatal period until delivery, after which the child was assessed regularly (See table 1). The sample populations of the animal research study included Wistar rats, pregnant females, and their male offspring.

Main findings

Throughout all the seven articles researched, various behavioral concerns were noted. These included some direct behavioral effects of prenatal cannabis exposure: decreased scores in reading ($p < 0.001$) and mathematics ($p < 0.02$) [21], increase in delinquent behaviors ($p < 0.01$) [22] and difficulty with externalizing issues [24,25]. Indirect or secondary effects of prenatal cannabis exposure, were, an increased risk of being arrested ($p < 0.001$) and lower educational goals or achievements ($p < 0.001$) [20], a decrease in emotional regulation measured through respiratory sinus arrhythmia (RSA) ($p < 0.05$) [23], depression, attention, and impulsivity [22,23,25].

Author	Number Exposed	Evaluation Age	Assessment Method	Direct Result	Indirect Result
Eiden., *et al*. (2018) [23]	247 children	9 months of age 24 months of age	Measurement of heart rate and RSA 5-min emotion regulation paradigm		Exposed children demonstrated greater emotional dysregulation ($p < 0.05$)
Goldschmidt., *et al*. (2016) [20]	608 children	3 years old 14 years old 16 years old 22 years old	Questionnaire Toddler Behavioral Checklist Diagnostic Interview Schedule-IV		38% of exposed children reported early-onset cannabis use which was linked to negative adult roles ($p < 0.04$) and an increased rate of conduct disorders ($p < 0.001$) at age 22.
Goldschmidt., *et al*. (2012) [21]	524 children	14 years old	Wechsler Individual Achievement Test	Exposed children showed decreased cognitive scores across reading, mathematics, and spelling ($p < 0.001$; $p < 0.02$; N.S)	
Da., *et al*. (2011) [22]	636 children	10 years old	Self-report Delinquency Scale Child Behavior Checklist Wide Range Assessment of Memory and Learning Children's Depression Inventory The Swanson, Noland, and Pelham	Exposed children demonstrated delinquent behaviors ($p<0.01$)	Exposed children showed increased rates of depression ($p < 0.001$), attention ($p < 0.01$), and impulsivity ($p < 0.01$).

Paul., *et al*. (2021) [25]	655 children	9-11 years old	The Child Behavior Checklist The Prodromal Questionnaire–Brief Child Version	Exposed children demonstrated a greater difficulty with externalizing behavioral problems ($p < 0.03$; $p < 0.02$)	Exposed children were associated with greater psychopathy, attention, and social issues ($p < 0.03$; $p < 0.02$).

Individualized results

Evidence level 2

Non-randomized control trials: Prospective studies

Eiden., *et al*. (2018) [23] conducted a study where a sample of mother-child dyads (n = 247) in their first trimester of pregnancy were assessed for exposure to cannabis and tobacco. The experimental group with exposure consisted of 181 mothers, while the controls of non-smokers were 77 mothers. Of the 181 tobacco smokers, 97 mothers also reported using cannabis. Prenatal substance use was measured through self-reports and biological assays of oral fluid samples. This study measured tobacco and cannabis use through the number of cigarettes or joints smoked per day. A demographic risk assessment was completed through 4 factors: maternal race, education, occupation, and partner status. At the 9-month assessment, the study completed a physiological assessment of reactivity and regulation, observed through various measurements such as heart rate (HR) and RSA. A higher score was indicative of a higher risk. Maternal dysregulation, psychological risk, and sensitivity were also taken into consideration through questionnaires during the 9-month assessment. At the 24-month stage, maternal sensitivity and infant emotional regulation were assessed using the 5-min emotion regulation paradigm [26].

Results indicated that infants in the exposed group demonstrated an increase in RSA in response to stress compared to infants in the control group who showed a significant decrease. The exposed group showed the increase in RSA was also associated with decreased toddler emotional regulation compared to the control group which showed an increase in emotional regulation. Maternal use of cannabis and tobacco was associated with lower maternal sensitivity at the 24-month stage and higher psychological risk. Additionally, higher maternal sensitivity during the 24-month stage was found to be associated with higher toddler emotion regulation [23]. This study could not establish any statistically significant direct effects, but, many indirect effects were documented regarding tobacco and cannabis exposure and toddler emotional regulation.

Goldschmidt., *et al*. (2016) [20] published data based on the longitudinal study of Maternal Health Practices and Child Development (MHPCD) where participants were monitored for 22 years, from the prenatal stage to 22 years post-partum. Data collection for the initial stage of research began in 1983 and was completed in 1986, until the 22-year phase from 2006 to 2009. The women were interviewed at various stages of gestation as well as stages post-childbirth with their child. Measures of newborn growth, cognitive development, behavior development, and drug use were assessed at each follow-up, along with demographic information. Two cohorts were included in the study and were compared to the control group with no use of each respective substance: women using cannabis and those using alcohol during pregnancy. The combined cohort then consisted of 763 live infant births. At the 22-year phase follow-up, roughly 80% (n = 608) remained in the study. Data from first-trimester cannabis use was used, measured by joints per day, as well as first-trimester alcohol use measured by average daily volume. At age 3, the offspring was assessed by the Toddler Behavior Checklist (TBC), completed by the mother to address anger, aggression, emotional instability, immaturity, and shyness. At this time, data on socioeconomics, general demographics, history of depression or anxiety, and maternal substance use were also collected.

At the 14-year phase, the children were questioned about their substance use history, paying special attention to cannabis use and frequency. This continued in the 16- and 22-year phases. Early cannabis use was defined as beginning before 15 years old. At age 16 the child was assessed for psychiatric or conduct disorders using the Diagnostic Interview Schedule-IV (DIS-IV) [27]. Finally, at age 22, the subjects were questioned about their personal lives, including career, marital status, highest education, military service, and the number of their children.

The questionnaire used at the 14, 16, and 22-year phases revealed that 38% of the young adults reported early onset cannabis use, with 67.5% who continued to use at the 22-year phase. At the 22-year phase, the subjects who admitted to early cannabis use were significantly less likely to have completed more than 12 years of schooling (37.2% vs. 54.5%, $p < 0.001$), and were more likely to have been arrested (56% vs. 27.3%, $p < .001$). This group was also less likely to have served in the military, be married, or have children by the 22-year follow-up. Those with higher score on the Toddler Behavior Checklist (TBC) results at age 3 were found to be linked to odds of early cannabis use ($p < 0.005$). The DIS-IV demonstrated an increase in lifetime conduct disorders in those who initiated cannabis use at an early age ($p < 0.001$). Other predictors of early cannabis use included prenatal cannabis exposure, prenatal tobacco exposure, and environmental risks at birth [20].

Overall, this study demonstrated the downstream effects of prenatal cannabis use and its link to early childhood behavioral issues and early onset cannabis use which has a known correlation with psychopathy and conduct disorders.

Reporting on the same MHPCD study, Goldschmidt., *et al*. (2012) [20] addressed specific difficulties in school achievements for the 14-year-old phase. At this phase, there were 524 mother-child dyads used in the study. Childhood depressive symptoms were measured by the Children's Depression Inventory (CDI) [28], IQ was measured using the Stanford-Binet Intelligence Scale (SBIS) fourth edition [29], attention was measured by the Swanson, Noland, and Pelham [30], and academic achievement was measured by Wechsler Individual Achievement Test (WIAT) Screener [31]. After considering all social factors, the results for the prenatal cannabis-exposed group showed a significant decrease in WIAT scores by roughly 2.9 points ($p < 0.05$), indirect effects on school achievement through negative SBIS score at age 6, as well as CDI depression scores and Swanson, Nolan, and Pelham (SNAP) Questionnaire inattention scores at age 10 [21].

This study, brought in the possible implications of early exposure to cannabis on the child's education, as well as the impact that disrupted behavior development has on schooling.

Day., *et al*. (2011) [22] reported on the same MHPCD study with a focus on the effect of prenatal cannabis exposure and the risk of delinquency. Although this study gathered data with additional prenatal alcohol exposure, the focus was maintained on the hypothesis regarding marijuana use or the purpose of this study.

There were various reports used to gather information from both the child and mother during these follow-ups. Firstly, the Self-report Delinquency Scale (SRD) questionnaire was used to assess concerning behaviors such as stealing, violence, cheating, and running away from home. Those adolescents who scored a one or higher were defined as delinquent while all others were given a score of 0. Additionally, the mothers were asked to complete the Child Behavior Checklist (CBCL) to assess 13 different items along the same lines lying, stealing, running away, and substance use. Other mediator tests performed at the 10-year follow-up point to assess neuropsychological performance, were CDI, the SNAP rating scale, and The Wide Range Assessment of Memory and Learning (WRAML) [22].

The average marijuana use reported in these groups during pregnancy was 0.4 joints per day (range 0-9). The births in this study included an 8% premature rate (<37 weeks gestation), and 10% small for gestational age (SGA). Based on this analysis of the SRD and CBCL, it was found that at 14 years of age, the adolescent with prenatal exposure was more likely to exhibit delinquent behavior. In the group of light marijuana users (n = 450) the rate of delinquency was found to be 44%, while in heavy users (n = 75) the rate was 61% (p <

0.01). The study aimed to control for significant environmental or socioeconomic effects in the multivariate analyses which still yielded a significant result for delinquency at age 14. The study concluded that the odds ratio was 1.76 for those exposed to one or more joints per day in utero, and double this in those who were heavily exposed. There were many mediated associations found with this data including increased rates of depressive symptoms ($p < 0.001$), and attention and impulsivity deficits ($p < 0.01$) which were measured through the CDI and SNAP evaluations [22].

Evidence level 3

Observational studies

Paul., *et al*. (2021) [25] recently published a study using data gathered from the ongoing longitudinal Adolescent Brain and Cognitive Development (ABCD) study. Data sets were collected from children aged 9 - 11 years old from June 1, 2016, to October 15, 2018. Three groups were created: cannabis exposure before knowledge of pregnancy (n = 413), cannabis exposure after knowledge of pregnancy (n = 242), and no exposure (n = 10,834). Various checklists and questionnaires were used to assess child internalizing or externalizing problems, attention, social issues, cognitive ability, sleep disturbances, as well as gestational age and birth weight. Covariates such as race, ethnicity, family history of psychopathy, and socioeconomic factors were included.

Before the covariates adjustment, prenatal cannabis exposure in both exposure groups showed an increase in psychotic-like experiences (PLEs), internalizing, externalizing, attention, social, and sleep problems, as well as a decrease in cognition compared to the no-exposure group (all $p < 0.03$). Prenatal exposure after known pregnancy only was also associated with LBW ($p < 0.002$). Post-covariates adjustment, the group with exposure after known pregnancy continued to be associated with higher PLEs, internalizing, externalizing, attention, and social problems ($p < 0.02$) [25].

El Marroun., *et al*. (2018) [24] completed a study where children (n = 5904) were assessed for emotional and behavioral issues at age 7 - 10. Participants in this study were exposed to maternal cannabis use during pregnancy, gathered through self-reports and urinary THC levels. This study also investigated the effects of maternal tobacco use and paternal tobacco and cannabis use. At age 9 years, the children completed the Brief Problem Monitor (BPM) questionnaire to assess behavioral and emotional issues. Additionally, mothers were asked to complete the Child Behavior Checklist (CBCL), and teachers submitted the Teacher Report Form (TRF). The study documented that roughly 30.2% of women stated daily consumption, 28.4% of women stated weekly, and 12.4% of women stated monthly cannabis consumption, while 29.0% of cannabis users did not report frequency of use. Internalized issues were measured based on evidence of emotional problems (i.e. anxiety or depression symptoms), and externalized based on evidence of behavioral issues (i.e. aggressive behavior or delinquency).

Based on the testing measures mentioned above, the results established an association between maternal cannabis use during pregnancy and teacher-reported externalizing problems in children (B = 0.55, 95% CI: 0.30 to 0.81), but not with internalizing problems (B = −0.06, 95% CI: −0.16−0.28). Paternal cannabis use was found to have similar results, reporting externalizing problems (B = 0.36, 95% CI: 0.22 to 0.49), but not internalizing problems (B = −0.07, 95% CI: −0.19 to 0.06). Similarly, the BPM self-reports outlined difficulty with externalizing problems (B = 0.48, 95% CI: 0.09 to 0.87), but not with internalizing problems.

Evidence level 0

Animal research study

Beggiato., *et al*. (2020) [19] published research where pregnant rats were treated with THC from gestational day 5 (GD5) through GD20. The rats were monitored through to adulthood where they were subjected to microdialysis in the medial prefrontal cortex to determine the kynurenic acid (KYNA) levels. In the brain, KYNA is a negative allosteric modulator of the α7 nicotinic acetylcholine (α7nACh) receptor and competitive inhibitor at the NMDA receptor, having a direct role in cognition. Researchers were interested in the relationship between prenatal THC exposure and increasing levels of KYNA which is known to have neuroactive properties. Abnormal KYNA levels have been shown to affect the levels of neurotransmitters involved in cognitive processes such as glutamate, dopamine, and GABA. The results of this study demonstrated that the offspring of the THC-treated rats had significantly increased levels of KYNA ($p < 0.05$), and decreased levels of glutamate ($p < 0.05$) in the medial prefrontal cortex once they reached adult age. Of note, before the maternal rats were euthanized, their plasma, as well as the fetal plasma and fetal brain levels of KYNA were normal, suggesting that there are more longstanding effects of KYNA on cognitive function [19].

Discussion

Significant results

Results from the seven research articles have provided satisfactory supplementary evidence supporting the hypothesis that prenatal cannabis exposure leads to behavioral problems in early childhood or adulthood, although a direct relationship is subjective. Therefore, the proposed hypothesis for this research was verified in a limited way, demonstrating more indirect outcomes of prenatal cannabis exposure.

There is strong evidence for early-onset use of THC having neurodevelopmental effects [32], and producing other long-term faulty decision-making behaviors [33], similar to the results of Goldschmidt., *et al*. (2016) [20]. These results, however, point towards early onset use in childhood or adolescence rather than prenatal exposure as the cause. Furthermore, many studies have reported significant negative birth outcomes such as an increase in hospital length of stay for these newborns with prenatal exposure [34], and low birth weight [35]. There is little evidence available, though, to establish the full scope of deficits seen with prenatal exposure in humans. This creates a greater concern for our pediatric population as data from research such as Skelton., *et al*. 2020 [36] have indicated a sharp increase in cannabis use in those states where it has now been legalized. Their study showed a significant increase in use during the prenatal period in legalized states compared to those states where cannabis was not yet legalized [36]. With the steady expansion of cannabis legalization or decriminalization around the world, we must understand and guide our pregnant population safely.

Three studies gathered data from the MHPCD longitudinal study and found direct and indirect associations between prenatal cannabis exposure and increased risk of delinquency, behavioral issues, and difficulty adapting to successful adult roles. Of the behavioral concerns, children at age 3 were found to specifically have higher rates of aggression and shyness, in the cannabis-exposed group [20], and lower IQ scores at age 6, predicting further difficulties in academic achievements at age 14 [21]. The study also demonstrated a direct association with delinquency and indirect associations with hyperactivity and impulsivity [22], depression, and behavioral deficits [21]. The study by Goldschmidt., *et al*. (2016) [20] suggested prenatal cannabis exposure led to early onset cannabis use, which ultimately showed an increased risk of conduct disorder and difficulty in adopting positive adult roles. The MHPCD study allowed us to take a look at several aspects of behavior over a prolonged period to outline various primary and secondary consequences of prenatal exposure to cannabis.

Another two studies supported an association between childhood externalizing problems such as delinquency, aggression, and populations of prenatal exposure. Although the findings in El Marroun., *et al*. (2018) [24] suggested that maternal cannabis use during pregnancy leads to childhood behavioral problems, these were also seen with maternal cannabis use before pregnancy and maternal tobacco use. The study, therefore, concluded that it is unlikely that there is a significant primary causal link between intrauterine cannabis exposure and childhood behavioral problems. Paul., *et al*. (2021) [25] evidenced similar results, where there was an increase in externalizing problems in children exposed to cannabis prenatally. This study provided more insight into the direct effects of prenatal cannabis exposure, particularly, a higher risk of psychopathy during childhood, as well as social and behavioral issues.

The study completed by Beggiato., *et al*. (2017) [19] demonstrated important implications of prenatal cannabis exposure to the prefrontal cortex in laboratory rats. Due to the challenges of controlling genetic and environmental factors in humans, it is difficult to prove a definitive causative link between cannabis use during pregnancy and its cognitive outcomes, so, the animal model studies are informative. This study used rat models to demonstrate the possible effects of cannabis use during gestation and its effect on brain development and cognition. Results showed an increase in KYNA, which has been linked to sensory gating, fear conditioning, and attention difficulties. This article also provided insight into the implication of early cannabis exposure and its connection to psychiatric diseases such as schizophrenia where levels of KYNA are already known to be increased [19]. Additionally, the results demonstrated a decrease in glutamate in the PFC. The prefrontal cortex plays an important role in various behavioral controls such as inhibition control for aggression. An imbalance of glutamate and GABA in the prefrontal cortex has been linked to various psychiatric diseases like anxiety, depression, and aggressive behaviors. Pharmacological studies have also demonstrated that antagonists of the NMDA receptors as seen with KYNA tend to cause an increase in episodes of aggression [37]. Again, this study was able to demonstrate how early exposure leads to detrimental effects in neurodevelopment, with the ability to cause various secondary effects later. Specifically, an animal study such as this one provides a deep look into the direct neurologic effect of cannabis on the developing brain, something that would be difficult to measure in the human population.

The study conducted by Eiden., *et al*. (2018) [23] revealed that children prenatally exposed to cannabis had a maladaptive response to stress compared to controls, which was demonstrated by an increase in RSA and HR. However, these results did not have a true statistical significance so the study concluded that this response could only prove a loose secondary association.

While these studies all mentioned an association between cannabis exposure and an increased risk of negative behaviors in the child, it is important to distinguish those direct and indirect outcomes to gain a full measure of this concern. In today's society, cannabis has now become less taboo and easier to access due to legalization in various countries, therefore the rates of use in all populations continue to rise, as demonstrated by Skelton., *et al*. (2020) [36]. There is, therefore, an urgent need for research to assist in understanding the long-term effects of this substance in many different circumstances, including pregnancy. While most healthcare professionals advise pregnant patients to stay clear of cannabis products, we require further research to understand the full direct ramifications on infant neurodevelopment.

Limitations

There are various limitations to these studies which should be factored in while completing an analysis. Due to the longevity of some of these studies, there are several opportunities for recall bias while interviewing subjects months to years after pregnancy. Additionally, there has been a large shift in recreational use and legalization, potentially decreasing the reliability of the results for today's population. The studies used in this review included a very specific population of low-income families which creates a limited generalizability to the general population. Finally, many of these studies included a multitude of substance use leading to possible confounding factors affecting the data.

Conclusion

As social changes are made around the world regarding cannabis legalization the importance of understanding its long-term consequences during the gestational period escalates. Many studies have demonstrated various indirect adverse behavioral outcomes due to prenatal cannabis exposure such as an increased risk of delinquency, aggression, and depression. However, there are limited known direct effects of cannabis exposure in utero which can create a space of inconsistency and doubt. As recreational cannabis use continues to grow around the globe, more surveillance and research are needed to provide quality care during the gestational period and to evaluate the consequences on the pediatric population.

Author Contributions

VG conceptualized the subject, reviewed the literature and wrote the draft manuscripts, designed the figures and table. JK assisted in the manuscript preparation. VG and JK finalized the manuscript. JK and JD contributed to the revision, editing, and proofreading of the final manuscripts. All authors contributed to the article and approved the submitted version.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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