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# Clearing the Smoke on Cannabis

## Cannabis Use During Pregnancy and Breastfeeding

### – An Update

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*This is the second in a series of reports that reviews the effects of cannabis use on various aspects of human functioning and development. This report focuses on maternal cannabis use during pregnancy and breastfeeding and its effects on children and young adults. It updates a previous report with new research findings that validate and extend our understanding of this issue. Other reports in this series address the effects on mental health, driving, respiratory and cardiovascular health, medical use, cognitive function and edibles. This series is intended for public health professionals, including program managers and coordinators, educators and health promoters, prevention experts, direct healthcare providers (e.g., physicians, nurses, pharmacists), policy and decision makers, and researchers.*

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## Key Points

- Cannabis is the second-most common psychoactive substance (after alcohol) used during pregnancy.
- Elements of cannabis can pass through the placenta and affect the fetus's development. Frequent cannabis use during pregnancy is associated with low birth weight and is part of a cluster of risk factors related to other adverse birth outcomes.
- There are also affects on behaviour in children and young adults, including attention deficits, emotional disturbances, increased hyperactivity and impulsivity, sleep disorders, and increased likelihood of substance use.
- Growing evidence from human and animal studies shows that paternal cannabis use can also negatively affect children's neurodevelopment.
- Elements of cannabis can pass into breastmilk during lactation, which the infant absorbs and metabolizes.
- The effects of cannabidiol (CBD) use during pregnancy or breastfeeding are unknown. Both clinical and preclinical studies are urgently needed to evaluate the safety of CBD use during pregnancy.
- Information on the effects of cannabis use during pregnancy is essential to help healthcare providers advise patients about the effect of cannabis use and improve the health and well-being of patients and their children.
- Pregnant or breastfeeding parents should have informed discussions with healthcare providers about the potential adverse effects of cannabis use during pregnancy to help them better understand the potential risks and help them make informed and healthy choices.

## Background

After alcohol, cannabis (also referred to as marijuana) is the most widely used psychoactive substance in Canada. According to the cross-sectional National Cannabis Survey, in 2020, 20.0% of Canadians aged 15 years and older reported using cannabis in the previous three months, and 7.9% reported daily use, a significant increase from 2018 (5.4%) and 2019 (6.1%) (Statistics Canada, 2021). The use of cannabis in 2020 was generally more prevalent among young people (15–24 years), with 19.2% of youth aged 15 to 17 years and 35.6% of young adults aged 18 to 24 years reporting use in the previous three months.

*Cannabis, also called marijuana, refers to products of the cannabis plant. It is usually a greenish or brownish material consisting of the dried flowering fruiting tops and leaves of the cannabis plant. Cannabis contains more than 100 cannabinoids, with delta-9-tetrahydrocannabinol (THC) being the main psychoactive ingredient responsible for the high that people feel. Cannabidiol (CBD) is the second-most common cannabinoid in cannabis. Cannabidiol is not associated with the high and is being studied for various medical applications, such as relieving pain, anxiety and other chronic conditions.*

A growing body of evidence suggests that cannabis use can negatively affect several aspects of people's lives, including mental and physical health, cognitive functioning, ability to drive a vehicle, and pre- and postnatal development among children. One in a series reviewing the effects of cannabis use on various aspects of human functioning and development (Gabrys & Porath, 2019; Konefal et al., 2019; Renard, 2020), this report explores the effects of prenatal cannabis exposure on offspring, including the birth outcomes, neurodevelopment processes, behaviour and mental health of children. Following a review of the evidence, we discuss implications for policy and practice.

Much of the available evidence on this topic comes from three prospective longitudinal cohort studies and four retrospective cohort studies. The longitudinal studies describe the effects of cannabis use during pregnancy on child development and behaviour. Table 1 summarizes these studies' details. The prospective longitudinal nature of these studies follows the same group of mothers and children over a long period. This allows for reliable measurement of the extent and timing of cannabis exposure, as well as many lifestyle variables (e.g., maternal health, socioeconomic status, maternal use of drugs other than cannabis) during pregnancy and assesses the developmental differences in children's behaviour and functioning.

**Table 1.** Summary of details from three longitudinal, prospective cohort studies evaluating outcomes of maternal cannabis use during pregnancy

| Variable | Ottawa Prenatal Prospective Study (OPPS) | Maternal Health Practices and Child Development (MHPCD) | Generation R |
|---|---|---|---|
| Reference | Fried et al., 1984 | Day et. al, 1992 | El Marroun et al., 2009 |
| Start year | 1978 | 1982 | 2001 |
| Location | Ottawa, Canada | Pittsburgh, USA | Rotterdam, Netherlands |
| Sample demographic | Caucasian, predominantly middle-class families | Mostly black women from low socioeconomic backgrounds | Multiethnic cohort with predominantly higher socioeconomic status |
| Total sample size | 583 | 763 | 7,452 |
| Initial sample size (cannabis exposed[a] during pregnancy) | 78 | 307 | 214 |
| Categorization of cannabis exposure | Irregular use (no more than one marijuana cigarette per week or 2nd hand smoke), moderate use (average 2–5 per week) or heavy use (average use greater than 5 per week) | Light use (between 0.0 and 0.4 average daily joints (ADJ), moderate use (between 0.4 and 1 ADJ) or heavy use (1 or more ADJ) | Occasional (monthly), moderate (weekly), heavy (daily) or no use |
| Times at which maternal cannabis use measured | Rate of use calculated at each trimester | Rate of use calculated at each trimester, and at 8 months, 18 months and 36 months postpartum | Rate of use calculated before pregnancy, in early pregnancy and in late pregnancy |

[a] Including women who also smoked tobacco and who may have only used cannabis during the first trimester.

The retrospective studies looked at past and archived data to examine the potential risk factors (including cannabis use) that could increase the risk for a disease. Those risks were compared between participants who were exposed and not exposed after the exposure and the outcome had already occurred. Table 2 summarizes the four most relevant retrospective cohort studies describing the effects of cannabis use during pregnancy on child development and behaviour. As these studies were conducted before Canada legalized recreational cannabis occurred in October 2018, the prevalence of cannabis use may have changed since then. More data needs to be collected to examine the effects of legalization on prenatal cannabis use.

## Prevalence, Reasons and Perceptions of Cannabis Use During Pregnancy

In Canada, about 47.6% of women of childbearing age (i.e., 15–44 years) reported lifetime use of cannabis in 2017 (Statistics Canada, 2019). In 2020, 23% of women aged 16–19 years, 20% of women aged 20–24 years and 19% of women aged 25 years and older reported daily or almost daily cannabis use in the past year (Health Canada, 2021c). Even more striking, in the northern territories of Canada such as Nunavut, 70% of women aged 15–19 years and 50% of women aged between 25 and 44 years have used cannabis in the past year (Reece & Hulse, 2020).

The Canadian Alcohol and Drugs Survey (CADS) showed that in 2019, 5% of women of childbearing age reported using cannabis during their last pregnancy, and 6% while breastfeeding (Health Canada, 2021a). Data from the Better Outcomes Registry & Network (BORN) database of live and stillbirths in Ontario between April 2012 and December 2017 showed that the prevalence of cannabis use during pregnancy increased by 61% from 1.2% in 2012 to 1.8% in 2017 (Corsi, Hsu et al., 2019). Increases in the prevalence of cannabis use during pregnancy were predominately observed among younger women aged 15 to 24 years (5.49%) and those with lower socioeconomic status (3.11%). Another recent study of 478 pregnant women in the greater Hamilton area, Ontario, showed that 4.2% of survey respondents reported using cannabis despite being aware of potential risks of harm for the fetus (Bartlett et al., 2020). Another recent survey from a women's health unit

**Table 2.** Summary of details from four retrospective cohort studies evaluating outcomes of maternal cannabis use during pregnancy

| Retrospective Cohort Study | ABCD (Winiger & Hewitt, 2020) | ABCD (Paul et al., 2020) | BORN (Corsi, Walsh et al., 2019) | BORN (Corsi et al., 2020) |
|---|---|---|---|---|
| Collection of data | June 1, 2016, to Oct. 15, 2018, from children born between 2005 and 2009 | June 1, 2016, to Oct. 15, 2018, from children born between 2005 and 2009 | Births and stillbirths between April 2012 and December 2017 | Births occurring between April 1, 2007, and March 31, 2012 |
| Location | 22 sites in the USA | 22 sites in the USA | Ontario | Ontario |
| Sample size | 11,875 | 11,489[a] | Matched cohort[b] of 98,512 records | Matched cohort[b] of 173,035 records |
| Cannabis exposed | 695 | 655 (413 were exposed only before maternal knowledge of pregnancy, 235 both before and after maternal knowledge, and seven only after maternal knowledge) | Matched group:[b] 5,639 cannabis exposed | Matched group:[b] 2,364 cannabis exposed |
| Cannabis exposure | Self-reporting ever using cannabis while pregnant | Self-reporting using cannabis either before maternal knowledge of pregnancy only, after maternal knowledge of pregnancy only or before and after maternal knowledge of pregnancy | Self-reporting ever using cannabis while pregnant during routine prenatal care | Self-reporting ever using cannabis during the first prenatal consultation (occurring between 11 weeks 2 days and 13 weeks 3 day of gestation) |

**Note.** ABCD = Adolescent Brain and Cognitive Development cross-sectional studies; BORN = Better Outcomes Registry & Network.

[a] Only participants with no missing records of cannabis exposure during pregnancy were included in this study.

[b] Matching strategy avoided critical potential confounders and ensured an equal distribution among exposed and nonexposed groups. In those studies, cohort samples were matched for maternal obstetrical and sociodemographic characteristics between reported cannabis exposed and nonexposed to reduce disparities in the sample.

in Canada showed that 5% of pregnant women and 6.3% of breastfeeding women were using cannabis regularly (daily or weekly) (Manning & Drover, 2020). A recent survey on maternal health of 7,111 women in Canada has shown that 3.1% of respondents reported using cannabis during pregnancy and 2.6% while breastfeeding (Grywacheski et al., 2021). Sociodemographic and mental health factors, including lower level of education, thoughts of self-harm, postpartum depression, anxiety symptoms or any combination of these were associated with cannabis use during pregnancy, breastfeeding or both. Finally, a study conducted in British Columbia showed that maternal cannabis use has increased over the past decade from 2.2% in 2008 to 3.3% in 2016 (Luke et al., 2019). Younger age, polysubstance use, lower socioeconomic status and history of mental illness were factors associated with cannabis use during pregnancy.

*There are different ways to use cannabis. Cannabis can be ingested (edible cannabis, oils, drinks, pills), inhaled (smoked or vaped) or applied to the skin. The duration of cannabis's effects depends on how it is used. When inhaled, cannabis intoxicating effects start within a few seconds to a few minutes and peak within 30 minutes. Effects can last up to six hours and residual effects can last up to 24 hours. When ingested, cannabis intoxicating effects do not kick in for about 30 minutes to two hours and peak at about four hours. The effects can last up to 12 hours after use and residual effects can last up to 24 hours. This timing differs from smoking or vaping cannabis, where the effects start to be felt within a few seconds or minutes and peak at about 30 minutes.*

Overall, the prevalence of cannabis use during pregnancy in several Canadian studies ranges from about 2% to 5% (Badowski & Smith, 2020). However, because prevalence measures largely rely on self-reporting, prevalence rates are likely underestimated due to stigma or other fears (i.e., child services intervention). For example, a study conducted in Pittsburgh found that only 36% of pregnant patients who tested positive for etrahydrocannabinol (THC) had disclosed their cannabis use (Chang et al., 2017). An older study analyzing the effects of prenatal cannabis and alcohol exposure on child academic performance at age 10 showed that 14% of women were using cannabis regularly (i.e., smoking one or more joints daily) during the first trimester of pregnancy, compared with 5.3% and 5.0% during second and third trimesters, respectively (Goldschmidt et al., 2012). Prevalence of cannabis use during pregnancy can be as high as 15% to 28% in disadvantaged, urban or low-income women (Beatty et al., 2012; Passey et al., 2014; Schempf & Strobino, 2008). Other recent studies have indicated that in the United States, younger age (before 25 years), lower education level, lower socioeconomic status (unemployment, lower income), being non-Hispanic or African-American, earlier trimester of pregnancy, marital status (i.e., not married), poor mental health (i.e., anxiety or depression) and concomitant use of tobacco, alcohol or both were risk factors for cannabis use among pregnant women (Bayrampour et al., 2019; Corsi, Hsu, et al., 2019; Odom et al., 2020).

In addition, with easier accessibility to cannabis, more legal product choices available and increasing social acceptance, the prevalence of cannabis use may have increased since the legalization of nonmedical cannabis in October 2018 in Canada. For example, cannabis use during pregnancy (confirmed by urine toxicology test) increased in California after legalization from 6% to 11% (Lee et al., 2020). Another study showed that the prevalence of cannabis use during pregnancy (confirmed by urine toxicology test) was as high as 18% in Colorado, which also legalized recreational cannabis (Rodriguez et al., 2019). In Ontario, Canada, a prospective longitudinal cohort study examined the consequences of nonmedical cannabis legalization a year following legalization (Turna et al., 2021). It showed that cannabis use decreased among adults who were using cannabis before legalization and increased among adults who were not using cannabis before legalization.

While the impact of legalization on cannabis use in Canada is not well established and more data need to be collected, the prevalence of cannabis use may have changed since the studies conducted before legalization.

## *Reasons for Cannabis Use During Pregnancy*

Over the past years, there has been an increasing belief that cannabis is harmless and can relieve some of the symptoms of pregnancy, such as morning sickness, nausea and vomiting, anxiety, and sleep disorders. This belief can be promoted by healthcare providers, the cannabis industry and nonmedical employees at retail cannabis dispensaries (Bayrampour et al., 2019; Dickson et al., 2018; Metz & Borgelt, 2018). For example, 69% of pregnant women in Colorado cannabis dispensaries were recommended cannabis to alleviate morning sickness (Dickson et al., 2018). It is also common for pregnant women to seek information about cannabis and pregnancy from family and friends, as

well as the internet and social media. However, a great deal of inaccurate information is circulating on untrusted online sources about the potential positive effects of cannabis on some of these pregnancy symptoms. As a consequence, many pregnant women report using cannabis during pregnancy to alleviate morning sickness, pain and mood disorders (Metz & Borgelt, 2018). In another survey conducted in Colorado, 63% of women reported using cannabis during pregnancy to alleviate anxiety and depression symptoms, and 60% reported using it for pain relief (Committee on Obstetric Practice, 2017). Similarly, in a Canadian women's health unit survey, among the 5% of pregnant women using cannabis, relieving anxiety symptoms (33.3%), sleep disturbances (22.2%) and nausea or vomiting (22.2%) were the most common reasons reported for cannabis use (Manning & Drover, 2020).

Despite these findings, there is no evidence showing that cannabis use during pregnancy can alleviate these symptoms. Further robust randomized controlled studies examining the efficacy of cannabis in alleviating symptoms associated with pregnancy as well as its safety during pregnancy are still needed. Meanwhile, increasing awareness about the potential risks of cannabis use during pregnancy and breastfeeding remains essential.

### *Perceptions of Cannabis Use During Pregnancy*

Pregnant women who use cannabis generally perceive cannabis as having low risks for the fetus, compared with pregnant women who do not use cannabis (Weisbeck et al., 2021). A survey of 306 women in the United States showed that 35% of pregnant women were using cannabis. Among those, 34% were not willing to quit cannabis use during their pregnancy. Three-quarters (75%) of pregnant women who were using cannabis were more likely to perceive cannabis use as harmless, compared with pregnant women who quit cannabis use (Mark et al., 2017).

In the 2021 Canadian Cannabis Survey, 83% of those who used cannabis did not agree that it was reasonable to use cannabis while pregnant or breastfeeding, which was the same as in 2020 (Health Canada, 2021b). That is compared with 88% of those who did not use cannabis in the previous 12 months, which was down slightly from 90% in 2020. In addition, 95% of women aged 16 to 50 years who had given birth in the previous five years reported not having used cannabis once they knew they were pregnant, which was unchanged from 2020. Finally, 92% of women reported not having used cannabis while breastfeeding their child, which was also unchanged.

Another recent survey from the greater Hamilton area in Ontario showed that most of the women surveyed were aware that cannabis can pass to the fetus through the placenta (94.3%) or to the infant through breastmilk (91.2%) (Bartlett et al., 2020). Both can have risks to the infant's development. However, despite this high proportion of aware women, 4.2% of them were still using cannabis while pregnant.

In a recent Canadian women's health unit survey, 22.6% of respondents said they believed that cannabis use during pregnancy and breastfeeding was harmless, while 30.4% were unsure of the potential harm of cannabis use during pregnancy and breastfeeding (Manning & Drover, 2020).

In the United States, a qualitative study examining attitudes and beliefs about prenatal cannabis use showed that pregnant women who used cannabis during pregnancy had conflicting attitudes about their cannabis use while pregnant (Chang et al., 2019). They reported trying to reduce cannabis use during pregnancy because of the potential risks for the developing baby. On the other hand, they perceived cannabis as being safer than other substances, including prescribed medications, because it is a natural plant.

Finally, an integrative review that analyzed women's perception showed that women who use cannabis during pregnancy generally perceived cannabis use as harmless compared with women who do not use cannabis (Bayrampour et al., 2019). Most pregnant women reported a lack of information or recommendations from and communication with their healthcare providers about the health effects of prenatal cannabis use. This reinforces the idea that cannabis use during pregnancy may be harmless or insignificant.

All these findings have implications for how healthcare providers discuss the use of cannabis with pregnant patients. Informed discussions with healthcare providers about the potential adverse effects of using cannabis during pregnancy are needed to help women make informed and healthy choices (Bayrampour et al., 2019). In addition, person-centred, harm reduction and trauma-informed approaches are needed during these discussions to help ensure informed and nonjudgmental discussions and build a trusting relationship between healthcare providers and pregnant patients.

## Effects on Pregnancy, Fetal Development and Birth Outcomes

### *Fetal Development and Neonatal Birth Outcomes*

After controlling for maternal tobacco, alcohol and illicit drug use and various demographic covariates, there is conflicting evidence of an association between cannabis

use during pregnancy and an increased risk of pregnancy complications, premature birth, small head circumference, small length, stillbirth or major congenital abnormalities (Gunn et al., 2016; Metz & Stickrath, 2015; National Academies of Sciences, Engineering, and Medicine, 2017). However, substantial evidence highlights an elevated risk for low birth weight in infants from mothers who used cannabis during pregnancy (National Academies of Sciences, Engineering, and Medicine, 2017). Further, while reports on the effects of prenatal cannabis exposure are mixed, heavy cannabis use is more strongly associated with certain adverse outcomes of pregnancy.

In the Generation R study, maternal cannabis use during pregnancy was associated with reduced fetal growth in mid and late pregnancy as well as a lower birth weight (El Marroun et al., 2009). These associations were independent of various lifestyle and socioeconomic factors. The results from this study also suggested a dose–response relationship such that heavier cannabis use during pregnancy was particularly associated with lower birth weight. Findings from the Maternal Health Practices and Child Development (MHPCD) study noted a small but significant negative relationship between cannabis use during the first trimester and length of the child at birth (Day et al., 1991).

In a study of a large cohort of Australian women presenting for public prenatal care at a large hospital between 2000 and 2006, Hayatbakhsh et al. (2012) reported that use of cannabis during pregnancy significantly predicted negative birth outcomes, including low birth weight, preterm birth, small for gestational age and admission to the neonatal intensive care unit. These effects were independent of the mother's sociodemographic characteristics, cigarette smoking, alcohol consumption and use of illicit drugs.

In contrast, the Ottawa Prenatal Prospective Study (OPPS) did not observe any differences in growth measures at birth between infants born to women using cannabis and those not using cannabis (Fried & O'Connell, 1987). Fried et al. (1984) noted a statistically significant reduction of about one week in the gestational age of infants born to mothers in the OPPS who used cannabis six or more times per week compared with those who did not.

Two recent meta-analyses assessed neonatal health outcomes following maternal cannabis exposure. The first included results from 24 studies that did not control for polysubstance use and found that exposure to cannabis in utero was associated with decreased birth weight and an increased likelihood of admission to the neonatal intensive care unit (Gunn et al., 2016). The second included results from 31 observational cohort or case-control studies where cannabis and other substance use had been recorded (Conner et al., 2016). The authors noted a significantly elevated risk of low birth weight and premature birth in women who used cannabis. That risk doubled when the frequency of cannabis use was at least once per week. However, these associations disappeared after adjusting for tobacco use.

Three retrospective cohort studies not included in these meta-analyses adjusted for concurrent tobacco use and reported mixed results on risks associated with prenatal cannabis exposure (Chabarria et al., 2016; Ko et al., 2018; Warshak et al., 2015). Chabarria et al. (2016) found that while smoking only cannabis had no significant effect on any of the birth outcomes assessed, both cannabis and tobacco were associated with an increased risk for low birth weight, preterm birth and decreased head circumference. Ko et al. (2018) only looked at mean infant birth weight and gestational age. After controlling for relevant covariates, such as cigarette smoking, they found no significant differences in infants from women who used cannabis during pregnancy. Warshak et al. (2015) reported an increased risk for admission to the neonatal intensive care unit and small for gestational age but no effect on birth weight. Smoking cannabis during pregnancy was also found to increase the odds of having an infant with low birth weight by almost three times, although authors did not adjust their analysis for tobacco or alcohol use (Campbell et al., 2018)

The large Ontario retrospective cohort study using the birth registry (BORN) examined the association between prenatal cannabis exposure and adverse maternal and perinatal outcomes (Corsi, Walsh, et al., 2019). Authors analyzed births and stillbirths among women aged 15 years and older between April 2012 and December 2017. They found that in women who reported cannabis use during pregnancy (1.4%), cannabis exposure was significantly associated with increased frequency of small for gestational age, placental abruption, greater transfer to neonatal intensive care and an abnormal five-minute Apgar score[1] of less than four.

In another recent study, cannabis use during pregnancy (among other substances use) was associated with an increased risk of small for gestational age (47% increased), preterm birth (27% increased) and intrapartum stillbirth (184% increased) (Luke et al., 2019). However, caution should be taken as the authors did not rule out the effects that other substance use may have had on pregnancy outcomes.

[1] The five-minute Apgar test is performed five minutes after birth on the newborn by the healthcare provider to examine different parameters such as breathing, skin color, heart rate, muscle tone and reflexes. The score indicates to the healthcare provider how the newborn is doing outside of the womb.

Finally, a retrospective observational cohort study was conducted using health records data from 3,435 women who received prenatal care and a subsequent singleton live birth in Minnesota. Among those women, 283 (8.2%) tested positive for THC via urine toxicology assays. Authors showed that exposure to cannabis during pregnancy was associated with small for gestational age and increased abnormal 12-month developmental screens (Kharbanda et al., 2020). Similarly, increased risk of small for gestational age was shown in another recent study in which prenatal THC exposure was also confirmed using urine analyses (Rodriguez et al., 2019).

In these studies, the authors concluded that the discrepancy in other findings evaluating the effects of prenatal exposure may be due to the uncertainty or underestimation of prenatal cannabis use. In support of this idea, a recent study showed that self-reported cannabis use during pregnancy (confirmed by urine toxicology testing) was associated with adverse outcomes, including preterm birth, hypertensive disorders of pregnancy, stillbirth or small for gestational age (Rodriguez et al., 2019). Importantly, the odds of adverse outcomes were higher in women who had more than one positive THC urine test compared with women who had negative THC tests. Using THC urine analyses to better confirm the use of cannabis during pregnancy would help to better estimate the effects of cannabis use during pregnancy.

Despite difficulties determining the unique effects of cannabis exposure on pregnancy and fetal development, the National Academies of Sciences, Engineering, and Medicine (2017) report concluded that there was substantial evidence for a statistically significant association between maternal cannabis smoking and low birth weight of infants exposed in utero. Low birth weights were subsequently associated with poor long-term outcomes throughout childhood and adulthood, including increased risk for Type 2 diabetes, hypertension, cardiovascular disease and respiratory problems (Gluckman et al., 2008; Statistics Canada, 2016).

However, it is yet unknown whether smoking as a means of use can have negative effects rather than cannabis itself. Cannabis smoking has been and still is the most common method of cannabis use. Therefore, some of the negative outcomes for infants of mothers using cannabis may be in part related to other toxic chemicals inhaled when smoking. To date, there have been no studies that have examined if different methods of cannabis use (smoking, vaping, sublingual or ingested) have different effects on fetal outcomes. Further studies are needed to explore this question.

### *Congenital Abnormalities*

Only a few correlational studies have demonstrated a link between congenital abnormalities and prenatal cannabis use. For instance, after adjusting for socioeconomic variables and the use of other substances such as tobacco and opioids, a recent study analyzing health record data in Canada found a positive correlation between rates of cannabis use and rates of congenital anomalies in the territories (Reece & Hulse, 2020). This included cardiovascular defects, orofacial clefts, Down syndrome and gastroschisis (a defect in an infant's abdominal wall). However, this finding should be treated with caution as this is a geospatial paper and many confounding factors were not considered.

Other studies have also shown potential associations between prenatal cannabis use and congenital anomalies, such as ventricular septal defects (Williams et al., 2004), bowel matting (Weinsheimer et al., 2008), gastroschisis, anencephaly and esophageal atresia (van Gelder et al., 2014).

Findings from the above-mentioned studies should be interpreted with caution because a "positive correlation" does not mean a "causal association" between prenatal cannabis use and offspring congenital anomalies. Confounding factors may have a role in this relationship, which may establish causality between prenatal cannabis exposure and congenital anomalies. Most of the available studies examining this relationship, including the prospective longitudinal birth cohorts, have not found an association between prenatal cannabis use and increased risk for congenital anomalies in children (Kharbanda et al., 2020).

#### *Regular and Heavy Cannabis Use*

*There is no single definition in the scientific literature of what constitutes regular cannabis use. The phrase generally refers to weekly or more frequent use over months or years and poses a risk for adverse health effects. Terms that are often used interchangeably with regular use include frequent use, chronic use and long-term use. By contrast, heavy use typically refers to daily or more frequent use and can be a sign of dependence and cannabis use disorder.*

## Effects on Neurocognitive Functioning and Neurodevelopmental Processes

### *Neurocognitive Functioning*

Findings from the OPPS and MHPCD longitudinal studies suggest that maternal cannabis use during pregnancy

affects children's neurocognitive development. Beginning at age three to four years, children of mothers who used cannabis heavily while pregnant have shown deficits in memory, verbal and perceptual skills, and verbal and visual reasoning after adjusting for potentially confounding variables[2] (Day et al., 1994; Fried & Watkinson, 1990). In contrast, the results from the Generation R study did not find evidence of such cannabis-related deficits when children were assessed at about three years old (El Marroun, 2010). Impaired verbal and quantitative reasoning and short-term memory have also been found in the MHPCD among six-year-old children whose mothers reported smoking one or more cannabis cigarettes per day while pregnant (Goldschmidt et al., 2008). Both the OPPS and MHPCD studies reported that in children about nine years of age, prenatal cannabis exposure was linked with impaired abstract and visual reasoning, poor executive functioning (i.e., visual-motor integration, nonverbal concept formation and problem-solving) and deficits in reading, spelling and academic achievement (Fried et al., 1998; Fried & Watkinson, 2000; Goldschmidt et al., 2004; Richardson et al., 2002). Vulnerability in visual-cognitive functioning has been shown to persist into early adolescence among those children heavily exposed to cannabis in utero (Fried et al., 2003).

Prenatal exposure to heavy maternal cannabis use during the first trimester also predicted significantly poorer scores on academic achievement tests (particularly in reading) at the age of 14 years in the MHPCD (Goldschmidt et al., 2012). Interestingly, these latter effects were found to be related to prenatal cannabis exposure on intelligence test performance at age six years, attention problems and

**Figure 1.** Neurocognitive and Behavioural Effects

| 18 months | 3–6 years | 9–11 years | 14–16 years | 17–22 years |
|---|---|---|---|---|
| Increased aggressive behaviour[c] | Deficits in verbal and perceptual skills,[a,b] verbal, quantitative and visual reasoning,[a,b] short-term memory,[a,b] attention[a,b] and vigilance[b] | Deficits in abstract and visual reasoning,[a,b] attention,[b,d] executive functioning,[a,b] reading,[a,b] spelling,[a,b] attention,[b,d] and internalizing, externalizing, and social behaviours[d] | Deficits in visual-cognitive functioning,[a] academic achievement,[b] information processing speed[b] and visual-motor co-ordination[b] | Deficits in executive functioning,[a] response inhibition[a] and visuospatial working memory[a] |
| Attention deficits (females)[c] | Hyperactivity[a,b] | Hyperactivity[a,b] | Delinquency[b] | Smoking[a,b] |
| | Impulsivity[a,b] | Impulsivity[b] | | Substance use[a,b] |
| | | Depressive and anxious symptoms[b] | | Early initiation of substance use[a,b] |
| | | Psychotic-like experiences[d] | | |
| | | Thoughts disturbances[d] | | |
| | | Long-term sleep disorders[e] | | |

[a] Ottawa Prenatal Prospective Study (Fried et al., 1984)

[b] Maternal Health Practices and Child Development (Day et al., 1992)

[c] Generation R (El Marroun et al., 2009)

[d] Adolescent Brain and Cognitive Development (Paul et al., 2021)

[e] Adolescent Brain and Cognitive Development (Winiger & Hewitt, 2020)

[2] In all three longitudinal studies, the analyses controlled for various covariates such as the children's gender and ethnicity, home environment, maternal socioeconomic status, prenatal exposure to tobacco and alcohol, and current maternal substance use.

depression symptoms at age 10 years and early start of cannabis use. At the age of 16 years, deficits in information processing speed, interhemispheric transfer of information and visual-motor coordination have been linked with prenatal exposure to cannabis (Willford et al., 2010) These effects were found with light to moderate prenatal cannabis exposure in the MHPCD. However, general intelligence does not appear to be affected by prenatal cannabis exposure (Fried et al., 1998; Fried et al., 2003).

Findings from brain imaging studies of young adults aged 18–22 years enrolled in the OPPS showed that in utero cannabis exposure negatively affects the neural circuitry involved in aspects of executive functioning, including response inhibition, attention and visuospatial working memory (Smith et al., 2004; Smith et al., 2006; Smith et al., 2016). Consistent with these findings, results from a neuroimaging study with the Generation R cohort showed altered brain morphology, specifically in the frontal cortex, in children aged 6–8 years who were exposed prenatally to cannabis (El Marroun et al., 2016). These findings are also consistent with a report of altered functional connectivity in neonates with prenatal cannabis exposure and are particularly noteworthy as they show that smoking cannabis during pregnancy can lead to long-term changes in children's neurocognitive development (Grewen et al., 2015).

In all three longitudinal studies mentioned above, the analyses controlled for various covariates, such as the children's gender and ethnicity, home environment, maternal socioeconomic status, prenatal exposure to tobacco and alcohol, and current maternal substance use.

Finally, the longitudinal Adolescent Brain and Cognitive Development (ABCD) study recruited children ages 9 to 11 years across the United States (Paul et al., 2021). Children in this study will be followed until age 20 years and will help characterize normal adolescent brain development and factors that can affect neurodevelopment. One of the ABCD cross-sectional studies examined whether prenatal cannabis exposure in 655 children exposed to cannabis prenatally before and after being aware of the pregnancy can be associated with psychopathology symptoms in middle childhood, such as psychotic-like experiences, internalizing or externalizing problems, attention deficits, thought disturbances and social behaviour problems (Paul et al., 2021). Cognition, sleep, birth weight, gestational age at birth, body mass index and brain structure (i.e., total intracranial volume, white matter volume and grey matter volume) were also analyzed. The researchers accounted for multiple confounding factors that were included in the ABCD cross-sectional studies. They included ethnicity (e.g., White, Black, Asian, Indigenous, Pacific Islander, Hispanic and other), first-degree familial history of psychopathology (e.g., depression, psychosis, anxiety, mania and antisocial behaviour), marital status, prenatal exposure to tobacco or alcohol, unplanned pregnancy, prenatal vitamin, alcohol or tobacco use, child sex, twin or multiple pregnancy, household income, birth weight, maternal age at birth, gestational age when pregnancy was discovered, child age and mother's education. Findings from this ABCD cross-sectional study showed that prenatal cannabis exposure after being aware of the pregnancy was associated with greater disturbances in attention, thought and social behaviours (Paul et al., 2021).

Conversely, a recent critical review of data from 45 longitudinal studies, including data from OPPS and MHPCD cohorts, investigated the effects of prenatal cannabis exposure on cognitive functioning in individuals aged from 0 to 22 years (Torres et al., 2020). The authors concluded that there were relatively few cognitive deficits observed in children who were prenatally exposed to cannabis. According to the authors, most studies that have shown cognitive deficits did not compare measures against a normative database that would have confirmed that findings were statistically significant. Normative data help characterize what is "normal" in a large, random and representative population at a specific period and include important other factors, such as age and education, for example.

### *Neurodevelopmental Outcomes*

A large Canadian retrospective cohort study using the birth registry (BORN) from Ontario, analyzed the relationship between cannabis use during pregnancy and neurodevelopmental outcomes in childhood (Corsi et al., 2020). The authors analyzed births occurring between April 1, 2007, and March 31, 2012. Their findings showed that prenatally cannabis exposed children had a 50% increased risk for an autism diagnosis even after controlling for confounding factors, such as income, preterm birth and the use of other substances (Corsi et al., 2020). However, these findings should be taken with caution as other residual confounding factors, such as genetic vulnerabilities, environmental factors, fetal and postnatal environment, and dose and type of cannabis used, might still play a role in this relationship, which ascertain causality between prenatal cannabis exposure and the onset of later childhood neurodevelopmental disorders (Corsi et al., 2020). The authors also pinpointed a small increased risk (11% to 22%) for developing intellectual deficits, learning disorders

and ADHD in prenatally cannabis exposed children compared with nonprenatally exposed children. However, these associations were no longer observed after controlling for confounding factors (Corsi et al., 2020).

## Behavioural Effects

### *Behavioural and Emotional Functioning Outcomes*

The behavioural effects of prenatal cannabis exposure have also been documented, although it is unclear as to how early such effects first present themselves. The Generation R study has reported that prenatal exposure to cannabis is associated with an increased risk of aggressive behaviour and attention problems as early as 18 months of age in girls, but not boys (El Marroun et al., 2011). At the age of four years, the OPPS failed to find evidence of a negative relationship between cannabis exposure and attention (Fried & Watkinson, 1990), whereas the MHPCD found impaired vigilance among exposed children at this age (Noland et al., 2005). When children reached age six years, the effects of maternal cannabis use during pregnancy become much more evident. Children who were prenatally exposed to cannabis — particularly those who were heavily exposed — were found to be more hyperactive, inattentive and impulsive compared with children who were not exposed prenatally to cannabis (Fried et al., 1992; Leech et al., 1999). At age 10 years, prenatally exposed children display increased hyperactivity, inattention and impulsivity, and show increased rates of delinquency and externalizing problems as reported by their mothers and teachers, compared with children who were not exposed prenatally to cannabis (Fried et al., 1998; Goldschmidt et al., 2000; Richardson et al., 2002). The MHPCD reported that children who were heavily exposed to cannabis during the first trimester (i.e., one or more joints per day) were almost twice as likely to display delinquent behaviour at the age of 14 years as the children who were not exposed to cannabis or those who were exposed to lesser amounts (Day et al., 2011). The authors also noted that the relationship between prenatal exposure to cannabis and delinquent behaviour appeared to be mediated by the effects of cannabis on depressive symptoms and by attention deficits in children exposed to cannabis. However, in children ages 13–16 years, the effects of prenatal cannabis exposure on some aspects of attention (i.e., flexibility, encoding and focusing) appeared to wane (Fried et al., 2003).

Similarly, another study assessed the potential causal association between prenatal cannabis exposure and behavioural or emotional functioning in Dutch children aged seven to 10 years (El Marroun et al., 2019). Findings showed that maternal cannabis use during pregnancy was associated with child externalizing behaviour problems, including harmful, aggressive or antisocial behaviours directed at others such as physical or relational aggression, delinquency, bullying, defiance and vandalism. However, both maternal cannabis use before pregnancy and paternal cannabis use were also associated with externalizing problems in children. This suggests that the association between prenatal cannabis exposure and behavioural or emotional functioning problems observed in children was not caused by direct in utero cannabis effects on fetal development but rather through residual confounding variables, such as shared genetic vulnerabilities, environmental factors, other variables such as parental behaviours, or any combination of these (El Marroun et al., 2019).

Consistent with this idea, a study showed that both prenatal tobacco and cannabis exposure were indirectly associated with child externalizing problems at 16 months of age, an effect potentially due to "harsh" parenting during caregiver–child interactions (Schuetze et al., 2019). These findings support other studies showing that regulation and externalizing behaviour problems in children may be associated with "harsh" parental behaviours, such as insensitivity, anger or hostility (Bradley & Corwyn, 2007; Gartstein et al., 2013; Kochanska & Knaack, 2003; Velders et al., 2011), behaviours that can be associated with cannabis use (Ansell et al., 2015). Therefore, these data suggest that beyond the potential direct effects of cannabis on fetal development, regular use of cannabis by one or both parents and associated parenting behaviours can also contribute to transgenerational behavioural or emotional problems.

### *Sleep Patterns*

The long-term effects of prenatal cannabis exposure on child sleep patterns were analyzed in another ABCD cross-sectional study (Winiger & Hewitt, 2020). After controlling for various confounding variables, the authors found that maternal prenatal cannabis exposure was associated with long-term sleep disorders, such as difficulty initiating and maintaining sleep, arousal disorders, irregular sleep–wake disorders and excessive drowsiness in children aged 9–10 years (Winiger & Hewitt, 2020).

These findings were consistent with another older study showing that prenatal maternal cannabis exposure was associated with long-term nocturnal sleep disturbances in children aged three years (Dahl et al., 1995), suggesting that in utero exposure to cannabis may have long-term negative effects on children's circadian regulation. Again, other residual confounding variables, such as shared genetic vulnerabilities, environmental factors or other

variables, such as parental behaviours, can also play a role in this relationship.

### *Substance Use*

There is also accumulating evidence that shows prenatal cannabis exposure may contribute to the start and frequency of substance use during adolescence. Animal studies showed that repeated exposure to THC in early development may enhance responses to other addictive substances later in life (Cadoni et al., 2001; Panlilio et al., 2013). Porath and Fried (2005) reported that 16- to 21-year-old children (particularly males) of women who used cannabis during pregnancy were at increased risk, in a dose-related manner, for starting and the daily use of tobacco and cannabis, compared with children of mothers who did not use cannabis during pregnancy. Similar results were noted by Day et al. (2006). At age 14 years, children of mothers who used cannabis heavily while pregnant not only reported using this substance more frequently than children of women who did not use it, but they also started using it at an earlier age. These findings were also evident when the offspring were 22 years of age (Sonon et al., 2015). The likelihood of cannabis use was related to the extent of prenatal exposure.

The long-term behavioural effects of maternal cannabis exposure may be particularly relevant in populations where other socioeconomic risk factors are also present. The continued use of cannabis by one or both parents in addition to parental attitudes toward cannabis can contribute to transgenerational trends in substance use.

## Effects on Children's Mental Health

### *Depressive and Anxious Symptoms*

Some evidence shows that in utero cannabis exposure can be associated with symptoms of depression and anxiety. After controlling for other drug use during pregnancy and risk factors for childhood depression, children of women using cannabis during pregnancy had significantly more depressive and anxious symptoms at age 10 years compared with children of women who did not use cannabis during pregnancy (Gray et al., 2005; Leech et al., 2006).

However, genetic and epigenetic mechanisms[3] can also contribute to an increased risk of psychiatric disorders, including anxiety and depression. For example, abnormalities in dopaminergic activity have been shown in humans exposed to cannabis in utero. The effect is believed to be mediated through epigenetic mechanisms in brain areas involved in anxiety and depression, such as the amygdala, nucleus accumbens and ventral striatum (DiNieri et al., 2011; Wang et al., 2004). Dopaminergic activity abnormalities are important neurobiological markers of psychiatric diseases, such as schizophrenia, anxiety and depression disorders.

A recent study has shown that maternal cannabis use was associated with increased anxiety, aggression and hyperactivity in early childhood (i.e., ages 3 to 6 years) as well as with the stress hormone, cortisol (Rompala et al., 2021). This behavioural phenotype was associated with decreased placental expression of important genes involved in immune function, including proinflammatory cytokines and immune cell–type markers. More studies are needed to better understand the relationships between maternal cannabis use, immune function and anxiety phenotype in children.

### *Psychotic Symptoms*

There is also some evidence that shows that prenatal cannabis exposure is associated with psychotic symptoms. For instance, data from the MHPCD study showed that young adults who were exposed prenatally to cannabis were 1.3 times more likely to display psychotic symptoms compared with unexposed young adults after controlling for other significant covariates (Day et al., 2015).

Consistent with these findings, a recent prospective cohort study analyzing data from the Generation R cohort examined the potential link between parental (maternal and paternal) cannabis use during pregnancy and the onset of childhood psychotic symptoms (Bolhuis et al., 2018). They found that both maternal and paternal cannabis use were associated with greater psychotic-like symptoms in children aged 10 years. They suggested the existence of other etiologic factors, such as genetics, environment or familial behaviours, rather than direct in utero mechanisms that may be involved in the relationship between parental cannabis use and the onset of psychotic experiences in children.

More recently, findings from the ABCD cross-sectional study showed that prenatal cannabis exposure after being aware of pregnancy was associated with greater psychopathology symptoms at ages nine to 11 years even after accounting for potentially confounding variables (Paul et al., 2021). The authors suggested that prenatal cannabis exposure may be associated with an increased risk of psychopathological symptoms, including psychotic-like experiences, and cognitive and social disturbances, in

[3] Epigenetic modifications are alterations in the expression of a gene and involve complex molecular mechanisms, such as DNA methylation and histone modification. Environmental factors, such as diet, stress, pollution, toxicants, substance use and inflammation, can play important roles in epigenetic modifications. Epigenetic modifications can lead to diseases, including cancers, autoimmune disorders, psychiatric diseases and diabetes.

middle childhood and concluded that pregnant women should avoid using cannabis.

The potential impact of prenatal cannabis exposure on the mental health of children is critical to their long-term health and well-being and needs to be examined more carefully in further longitudinal studies.

## Breastfeeding

Breastfeeding provides many health benefits to the development of an infant, but these benefits must be weighed against any potential risks resulting from exposure to cannabis during lactation. Concerns about the use of cannabis during lactation stem from observations in humans showing that THC is secreted in breastmilk (de Oliveira Silveira et al., 2017; Garry et al., 2009; Marchei et al., 2011; Merritt et al., 2016; Metz & Stickrath, 2015) and is also absorbed, metabolized and excreted by the infant (Djulus et al., 2005; Garry et al., 2009; Liston, 1998; Perez-Reyes & Wall, 1982).

In addition to THC, cannabidiol (CBD) can also be found and can accumulate in breastmilk after maternal cannabis inhalation or edible ingestion (Moss et al., 2021). This is because cannabinoids are highly lipophilic compounds and can be stored in breastmilk, which is a rich source of healthy fats. Cannabinoid levels found in breastmilk mostly depend on the dose and frequency of maternal cannabis use.

One study estimated that within four hours after a single inhalation of cannabis, breastfed infants ingest about 2.5% (range from 0.4% to 8.7%) of the maternal dose of THC (Baker et al., 2018). Another older analysis calculated an infant's exposure to THC through ingestion in one feeding to be 0.8% of the mother's consumption (Bennett, 1996). Other studies have shown that THC levels can stay in breastmilk from six days to six weeks following maternal cannabis use, with a THC half-life estimation of 20 days (Bertrand et al., 2018; Cannabis, 2021). A prospective, observational pharmacokinetic study estimated the amount and duration of THC levels in breastmilk of 25 women who used cannabis while pregnant and gave birth between Nov. 1, 2016, and June 30, 2019 (Wymore et al., 2021). Data showed that, among seven women who self-reported abstinence from cannabis (which was confirmed by plasma analysis), the estimated half-life of THC in breastmilk was 17 days, with an estimated elimination time greater than six weeks. Therefore, the idea of "pumping and dumping" breastmilk right after maternal cannabis use to reduce infant cannabis exposure during breastfeeding does not seem to be relevant.

The effects of maternal cannabis exposure on infants through breastmilk are not well studied. The potential long-term effects of such exposure on an infant's developing brain are still poorly documented and any conclusions are generally confounded by in utero cannabis exposure. Several reports suggest that the use of cannabis during breastfeeding contributes to negative short-term effects on infants, including sedation, lethargy and poor feeding habits (Djulus et al., 2005; Liston, 1998; Miller, 2012). Two limited studies with very small sample sizes have attempted to examine the isolated effects of cannabis exposure through breastmilk on long-term infant health and development. The first study reported that occasional use of cannabis during lactation did not affect motor and mental development after one year (Tennes et al., 1985). The second study suggested THC exposure through breastmilk in the first month after birth could be associated with decreased motor development at age one year (Astley & Little, 1990). Neither study adequately controlled for prenatal exposure to THC.

Finally, breastfeeding encourages maternal behaviour and bonding between the mother and infant. Maternal consumption of cannabis can compromise mother–infant bonding,

***What is the endocannabinoid system?***

*The brain produces its own natural compounds, called endocannabinoids, which act like THC. Endocannabinoids, which include anandamide (AEA) and 2-arachidonoylglycerol (2-AG), bind to cannabinoid (CB1 and CB2) receptors. Cannabinoid receptors are throughout the brain and body, meaning that cannabinoids can influence a broad range of psychological and biological processes, such as cognition, emotional processing and regulation, stress response, appetite, immune functioning, the endocrine (hormone) system, sleep and pain signalling (Zou & Kumar, 2018). CB1 receptors are more concentrated in the brain. THC can mimic the activity of AEA and bind to the CB1 receptors to exert its psychoactive effects. However, THC binds CB1 receptors at much higher levels than AEA, flooding the endocannabinoid system, leading to altered functioning of each process. This flooding means that chronic use of cannabis (i.e., repeated brain exposure to THC) can alter the functioning of the endocannabinoid system, which can include changes in AEA and 2-AG activity, and the distribution of cannabinoid receptors (Jacobson et al., 2019).*

which may contribute to children's neurodevelopmental alterations later in life (Best Start Resource Centre, 2017; Shieh & Kravitz, 2006). For example, recent studies have shown that postnatal maternal cannabis use was associated with a shorter breastfeeding duration compared with women who did not use cannabis postpartum (Crume et al., 2018; Ko et al., 2018). In addition, because cannabis affects alertness, understanding and judgment, its use can also compromise parent–infant interactions (Best Start Resource Centre, 2017; Centre of Excellence for Women's Health, 2017; Sachs et al., 2013).

Breastfeeding mothers should also consider harms associated with second-hand cannabis smoke, which is especially harmful for infants and young children (Best Start Resource Centre, 2017; Centre of Excellence for Women's Health, 2017; Colorado Department of Public Health and Environment, 2017; Wilson et al., 2017). Even though data on the effects of second-hand cannabis smoke are still emerging, experts recommend pregnant and breastfeeding women avoid cannabis smoke as it contains many of the same harmful chemicals as tobacco smoke, which has the potential to harm a developing baby (Public Health Agency of Canada, 2018).

In the absence of sufficient evidence for an association between cannabis use during lactation and health outcomes for the infant, using cannabis during lactation is discouraged due to potential risks (Committee on Obstetric Practice, 2017; Reece-Stremtan & Marinelli, 2015; Society of Obstetricians and Gynaecologists of Canada, 2022). Further research is needed to fully evaluate the influence of cannabis on maternal behaviour and the impact of this influence on child development and outcomes. In addition, if women choose to continue using cannabis during pregnancy, harm reduction strategies such as encouraging them to use methods of cannabis consumption other than smoking would be beneficial.

## Mechanisms of Action

In the human fetal brain, endogenous cannabinoid CB1 receptors (CB1Rs) are found as early as 14 weeks of gestation (Biegon & Kerman, 2001), with drastic changes occurring in their expression throughout the gestational period in different brain areas, notably the limbic structures, which are involved in emotional regulation (Mato et al., 2003). Similarly, both endocannabinoids AEA and 2AG are found in the fetal brain, with concentration levels varying throughout the perinatal period. That suggests an important role of the endocannabinoid system during the development of the fetal brain (Friedrich et al., 2016). Many studies have confirmed that CB1Rs and endocannabinoids play crucial roles during fetal development by controlling neurodevelopmental processes involved in the development of neurons and synapses (Berghuis et al., 2007; Harkany et al., 2007; Maccarrone et al., 2014; Mulder et al., 2008).

The characteristic lipophilic nature of cannabinoids allows them to cross the placental and blood–brain barrier where they can activate cannabinoid receptors (Park et al., 2003). Therefore, exposure to exogenous cannabinoids in utero may disrupt the fetal endogenous cannabinoid signalling system and consequently the embryo development. Supporting this idea, a study in humans has shown that prenatal THC can directly and permanently impair the neuronal networks during fetal brain development, an effect potentially mediated via CB1Rs (Tortoriello et al., 2014). Studies in humans have also demonstrated that prenatal cannabis exposure may lead to alterations in various neurotransmitter (i.e., GABAergic 3, dopaminergic, glutamatergic, serotonergic and opioidergic) systems in children (Fernández-Ruiz et al., 2000; Jutras-Aswad et al., 2009; Trezza et al., 2008).

## Paternal Cannabis Use

Over the years, a growing interest in the effects of prenatal paternal use of cannabis on offspring has emerged. For example, the Generation R and ABCD cohorts pinpointed that paternal cannabis use during the gestational period, independently of maternal cannabis use, can be associated with the onset of psychotic-like experiences and other behavioural disorders in middle childhood (Bolhuis et al., 2018; Paul et al., 2021). Whether those effects are induced by epigenetic mechanisms or other underlying etiological factors remains unclear.

Studies in animals have provided further information about the long-term effects of paternal cannabis use on offspring: One study showed that adolescent THC exposure in rats before mating can lead to lasting behavioural and neurobiological abnormalities on the next generation of rats that have been unexposed to THC. This suggests that THC can affect parental gametes and have lasting negative effects on the next generation of rats (Szutorisz et al., 2014). Supporting this idea, recent evidence coming from human and animal studies suggested that paternal THC exposure can alter sperm cells' DNA methylation, therefore influencing offspring genes and development (Murphy et al., 2018). Another study in rats found that while premating paternal THC exposure did not have negative effects on birth weight, survival and growth of the offspring, it induced long-term attentional and cognitive deficits when offspring were tested at adolescence (Holloway et al., 2020) or adulthood (Levin et al., 2019).

Therefore, besides potential direct in utero effects, prenatal THC exposure can impact the developing brain and behaviour via action on gametes, or through epigenetic modifications such as DNA methylations or histone replacement that can modulate gene expression and influence protein production (Cholewa-Waclaw et al., 2016; Maze et al., 2014). Further studies need to be conducted to better understand epigenetic mechanisms potentially associated with behavioural and developmental disorder outcomes in offspring exposed to maternal or paternal cannabis use.

## Effects of Cannabidiol During Pregnancy

The effects of CBD use during pregnancy or breastfeeding are unknown. Both clinical and preclinical studies evaluating the safety of CBD use during pregnancy are urgently needed, especially with the widespread belief that CBD can relieve symptoms associated with pregnancy (i.e., pain, nausea, vomiting, anxiety).

CBD products often contain THC, which is known to have negative effects on brain development. There is no clinical evidence yet about the safety of using CBD during pregnancy, and only a few studies on animals have analyzed the effects of CBD during pregnancy and lactation. For example, in one older study on rodents, it was shown that maternal exposure to CBD reduced spermatogenesis and fertility in male offspring examined at adulthood (Dalterio & DeRooij, 1986). In a more recent study, Wanner et al. (2021) found that maternal use of CBD in mice induced long-term anxiety and cognitive deficits in females but not in male offspring. These effects were associated with changes in genes through epigenetic modifications that play important roles in neuronal function and are known to be involved in psychiatric and neurodevelopmental disorders. This preclinical study was the first to identify potential long-term negative effects induced by maternal prenatal CBD in female offspring.

Further studies are needed to better evaluate the effects of CBD use during pregnancy and breastfeeding. While we are waiting for more robust studies, the Society of Obstetricians and Gynecologists of Canada (2022) recommended that women should not use cannabis or CBD during pregnancy or breastfeeding.

## Conclusions and Implications

Brain development involves a complex cascade of events influenced by prenatal, physical, social and emotional factors early in life, which can have long-lasting effects on behaviour (for reviews, see Finnegan, 2013; Leyton & Stewart, 2014). Maternal cannabis use can directly affect the prenatal brain and significantly disrupt neural development, leading to adverse effects on child development and brain function, including cognition, emotions and memory impairments. Cannabis use during pregnancy and breastfeeding does not appear to be harmless, and there is growing evidence showing some risks associated with cannabis use on fetal development. Indeed, the evidence shows that prenatal cannabis smoking (particularly heavy exposure) has adverse effects on cognitive functioning, behaviour, mental health and substance use beginning as early as age three years and during adolescence.

However, there are some limitations in the available data. First, many studies do not indicate a gestational age of exposure, cannabis type, frequency of use, dose and method of use, and they often rely on self-reported cannabis use, which can be inaccurate or underreported. Self-reports of cannabis should be validated in further studies using urine toxicology tests.

Conclusions about the effects of prenatal cannabis exposure can be confounded by other maternal risk factors that tend to occur more frequently in women who use cannabis. These factors include lower prenatal care access, poor nutrition, poor physical and mental health, lower socioeconomic status, lower levels of education and the use of other substances. Negative perinatal outcomes appear more pronounced in infants when mothers smoked both cannabis and tobacco compared with the use of either substance alone, suggesting an additive effect of using cannabis with tobacco (Chabarria et al., 2016; El Marroun et al., 2009). While not yet corroborated by evidence in humans, animal studies also suggest that cannabis and alcohol during pregnancy can also have synergistic effects (Hansen et al., 2008; Seleverstov et al., 2017; Subbanna et al., 2018).

While prospective longitudinal studies are better able to assess and adjust for some of these factors to parse out direct associations with prenatal cannabis exposure, some other studies do not. Because of the existence of other potential confounders, the effects of prenatal cannabis exposure can be difficult to attribute only to cannabis, so data should be interpreted with caution. Future studies should assess and control for confounding variables that can potentially influence the development of prenatally exposed offspring. Additionally, most of the studies reported only positive correlation or associations between prenatal cannabis use and offspring negative outcomes. Positive correlation or association does not mean causal association. Findings from studies should be interpreted with caution.

Over the years, cannabis THC content from smoked cannabis has considerably increased from 3% to 6% in prior decades to 5% to more than 15% (Hall et al., 2019). Discrepancies in findings about birth, behavioural and developmental outcomes among studies might be attributed to the increasing potency of cannabis over the past few decades (ElSohly et al., 2016; European Monitoring Centre for Drugs and Drug Addiction, 2017; University of Mississippi, National Center for Natural Products Research [as cited in Executive Office of the President of the United States, 2013]; Mehmedic et al., 2010). This possibility is especially relevant for comparisons among the OPPS, MHPCD and the more recent Generation R studies as the children enrolled in the latter study may have been exposed to higher levels of THC.

In addition, authorized retail cannabis stores can be of concern because of varying THC levels in the available products. For example, in some cannabis concentrates made by extracting THC from the plant such as kief, hash or resin, THC content ranges from 39% to 90%. However, the legalization of nonmedical cannabis allows consumers to know exactly the content of the product they are using and select lower-risk products (e.g., containing less THC). On the illegal market, there is no guarantee of the THC levels nor any other potentially harmful contaminants. Strong evidence-based information should be incorporated into the training of retail cannabis staff, so they can better inform customers about the potential effects of cannabis use during pregnancy and breastfeeding. However, there is no determined amount of cannabis exposure that is safe. Until the effects of prenatal cannabis exposure are well understood, the safest option available to pregnant women is to avoid using cannabis (Best Start Resource Centre, 2017; Canada FASD Research Network, 2017).

Growing evidence from human and animal studies has shown that both maternal and paternal cannabis use can have negative outcomes on offspring neurodevelopment, and these effects can be linked with the existence of shared etiological factors, such as genetic and environmental, familial behaviours, lifestyle habits of the parents and so on. Further robust clinical studies with both parents along with increased awareness of potential health outcomes associated with prenatal cannabis use are crucial to understanding the potential risks of cannabis use during pregnancy.

Cannabis use for therapeutic purposes, including CBD use, during pregnancy or lactation is also not recommended. In addition, while consuming cannabis in edible or vaporized forms eliminates the risks of smoking, the child will still be exposed to the components of cannabis (Colorado Department of Public Health and Environment, 2017). The Society of Obstetricians and Gynecologists of Canada (2022) recommends that women should not use cannabis or CBD products during pregnancy or breastfeeding. An investment in public education efforts to increase awareness of the effects of cannabis use during pregnancy is needed. This investment would be useful considering that online media frequently report benefits of cannabis or CBD use that are not consistent with scientific evidence. Such reports include the portrayal of cannabis use as helpful for pregnancy symptoms, such as morning sickness (Jarlenski et al., 2018).

### *Implications for Healthcare Professionals*

Despite the high prevalence of cannabis use among women of childbearing age, the potential affect of cannabis on the developing brain and the long-term influence on cognition, behaviour and mental health are still not well-appreciated by society. Healthcare professionals who provide care to pregnant women should be well informed of the latest clinical evidence and research to advise pregnant women and those of childbearing age of the potential risks. Healthcare professionals need to explore these issues with patients and provide unbiased, compassionate information to women and their partners. Appropriate counselling services should also be offered to nursing mothers who are using cannabis as the benefits of breastfeeding can still outweigh the possible harms of exposure from occasional cannabis use (Djulus et al., 2005; Garry et al., 2009).

However, there are growing concerns that the medical community does not have sufficient guidance for addressing maternal cannabis use during pregnancy nor breastfeeding, and there is a strong need for training in the management of cannabis use during pregnancy. Improved communications and guidance from healthcare providers and resources addressing maternal cannabis use during pregnancy or breastfeeding are therefore strongly needed. There is also a need for person-centred, harm reduction and trauma-informed approaches to discuss cannabis use during pregnancy and breastfeeding and building a non-judgmental and trusting relationship between healthcare providers and pregnant parents.

Prevention efforts aimed at reducing prenatal cannabis exposure could be aided by clinical guidelines developed for healthcare practitioners about discussing the health effects of cannabis use during pregnancy and breastfeeding, such as those available in Colorado (Colorado Department of Public Health and Environment, 2017). The Society of Obstetrician and Gynaecologists of Canada is working on clinical guidelines that will provide healthcare workers with the latest evidence on cannabis use and women's health,

with a focus on women who are planning a pregnancy, who are pregnant or who are breastfeeding.

### *Implications for Researchers*

More research on both maternal and paternal cannabis use during pregnancy is needed. Knowledge gaps exist about reporting quantity and quality of cannabis used, CBD effects, impact of consumption method, timing of use in pregnancy and effect on breastfeeding. The changing landscape, including increased accessibility to cannabis, decreased perceptions of risk, increased THC concentrations in cannabis and the advent of potent synthetic cannabinoid products, needs to be examined. Finally, research and prevention efforts should explore the role played by the parental determinants of health (Brown et al., 2016; Havens et al., 2009; Passey et al., 2014). Addressing these comorbid conditions needs to be part of a holistic approach to reducing the risks associated with cannabis use during pregnancy and breastfeeding.

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