Peri-Pregnancy Cannabis Use and Autism Spectrum Disorder in the Offspring: Findings from the Study to Explore Early Development

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Abstract

The association of autism spectrum disorder (ASD) with self-reported maternal cannabis use from 3 months pre-conception to delivery ("peri-pregnancy") was assessed in children aged 30–68 months, born 2003 to 2011. Children with ASD (N = 1428) were compared to children with other developmental delays/disorders (DD, N = 1198) and population controls (POP, N = 1628). Peri-pregnancy cannabis use was reported for 5.2% of ASD, 3.2% of DD and 4.4% of POP children. Adjusted odds of peri-pregnancy cannabis use did not differ significantly between ASD cases and DD or POP controls. Results were similar for any use during pregnancy. However, given potential risks suggested by underlying neurobiology and animal models, further studies in more recent cohorts, in which cannabis use and perception may have changed, are needed.

Keywords Cannabis · Marijuana · Epidemiology · Autism spectrum disorder

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Self-reported past-month cannabis use among pregnant women in the U.S. increased significantly between 2002 and 2014 from 2.4 to 3.9% (Brown et al., 2017). In 2017, 9.8% of recently delivered U.S. women used cannabis in the 3 months before pregnancy and 4.2% during pregnancy (Ko et al., 2020). The perceived therapeutic effects of cannabis for morning sickness and uncertainty about its adverse perinatal consequences contribute to use during pregnancy (Bayrampour et al., 2019). Among pregnant U.S. women, the percentage who perceived "no risk" of harm from smoking marijuana once or twice a week increased from 3.5 in 2005 to 16.5% in 2012 among those without recent cannabis use, and from 25.8 to 65.4% among those with recent use (Jarlenski et al., 2017).

While there is consistent evidence that maternal cigarette smoking leads to histopathologic changes in the fetal brain and that carbon monoxide may play a role in cognitive and neurobehavioral deficits in offspring of smokers (U.S. Department of Health & Human Services, 2010), less is known about neurodevelopmental consequences of maternal cannabis use for the fetus. In animal models, prenatal or early life exposure to cannabis results in persistent changes in cognitive performance, behavior, and stress response (Roncero et al., 2020). Longitudinal studies of offspring with in utero cannabis exposure have reported subtle deficits in impulse control, attention and executive functioning starting around 3–4 years of age and continuing into adolescence and beyond (Day et al., 1994; Fried & Watkinson, 1990; Griffith et al., 1994; Metz & Borgelt, 2018; Roncero et al., 2020). These cohort studies have not (to date) reported on associations between prenatal cannabis use and subsequent diagnosis of ASD.

A large population-based retrospective cohort study using a Canadian birth registry found that children whose mothers had cannabis use recorded at the first prenatal visit were 50% more likely to have an ASD diagnosis during a median 7.4 years follow-up than children without recorded cannabis exposure, after controlling for confounding (Corsi et al., 2020). Cannabis use was recorded for just 0.6% of mothers, a much lower prevalence than in the US, which may reflect different patterns of use in pregnancy. Further, no information about cannabis use either preconception or in later trimesters was collected.

The objective of this analysis was to examine the association of maternal cannabis use prior to conception and throughout pregnancy with ASD in preschool-aged children enrolled in the Study to Explore Early Development (SEED). SEED provides both developmentally-disabled and typically-developing study groups for comparison, enabling differentiation of effects specific to ASD from those more generally affecting neurodevelopmental disorders.

Methods

Study Design

SEED is a multi-site case–control study that examines phenotypic characteristics and environmental and genetic risk factors for ASD (Schendel et al., 2012). Cases were children who met study criteria for ASD (detailed below). Two control groups comprised children from the general population (POP) and children with non-ASD developmental delays/disorders (DD) (e.g., language or motor delay). The study was approved by institutional review boards at the Centers for Disease Control and Prevention and each study site. Written informed consent was obtained from all families.

Participants

Eligible children were born September 2003 to August 2006 (SEED1) or January 2008 to December 2011 (SEED2) in a study catchment area in California, Colorado, Georgia, Maryland, North Carolina, or Pennsylvania. The two birth cohort time periods were based on separate funding cycles for enrollment and data collection. At enrollment, eligible children were 24–68 months old and lived in the same catchment area with their caregiver aged ≥ 18 years who had continuously cared for the child since age 6 months and spoke English or, at two sites, English or Spanish. Study sites have been described elsewhere (DiGuiseppi et al., 2016; Schendel et al., 2012). To limit inaccurate recall of events in pregnancy and early life while allowing diagnostic accuracy for ASD and appropriate age ranges for validated study instruments, children were clinically evaluated at 30–68 months of age. Children were recruited for ASD and DD groups from educational and clinical settings serving children with developmental delays or disorders, and for the POP group from randomly sampled birth certificates at each site.

Data Collection, Study Group Classification and Key Variables

Data collection for all three groups included interviews, self-administered forms, the Social Communication Questionnaire (SCQ) (Rutter et al., 2003) and Mullen Scales of Early Learning (MSEL) (Mullen, 1995). The SCQ was used to identify possible undiagnosed ASD, defined as a score ≥ 11 (Allen et al., 2007). Children considered at risk for ASD based on SCQ score ≥ 11, previous ASD diagnosis, or observed ASD symptoms during the MSEL, regardless of source population, underwent confirmatory assessments, including the Autism Diagnostic Observation-Schedule (ADOS) (Lord et al., 1999) and Autism Diagnostic

Interview-Revised (ADI-R) (Gotham et al., 2007). Children meeting cutoff scores on these instruments were classified as ASD (Schendel et al., 2012; Wiggins et al., 2015). Children recruited from educational and clinical settings with a prior diagnosed developmental condition who were assessed for ASD but did not meet cutoff scores were excluded from this analysis, while those not at risk for ASD as defined above were classified as DD controls. Children recruited from the birth certificate sample (excluding those identified with ASD) were classified as POP. This analysis only included children who completed a clinic visit for developmental assessment.

Data on the family, child, and household were collected. The biological mother was interviewed about drug use during pregnancy; children whose mothers did not respond to these questions were excluded. Mothers were asked, "Between three months before the start of the pregnancy till the time of delivery/the cessation of breastfeeding, did you use any of the following recreational or street drugs?" Mothers who said "yes" to any drugs were asked about their use in each month from 3 months before pregnancy through delivery (categorized into pre-conception, first, second and third trimester) and during breastfeeding. "Peri-pregnancy" cannabis use was defined as any use from 3 months before pregnancy through the third trimester. "During pregnancy" was defined as cannabis use during any trimester and "during breastfeeding" as any use while breastfeeding. Data were also collected on maternal use of tobacco, alcohol, and other illicit drugs (including prescription drugs not prescribed to the mother) at any time during the peri-pregnancy period (Yes/No for each substance). Socio-demographic factors included child age at enrollment, child sex, maternal race/ethnicity and level of education at delivery, and annual household income in the year before pregnancy, categorized as shown in Table 1. Sociodemographic variables were missing for < 1% of participants, except for race/ethnicity (2% missing) and household income (3% missing).

Statistical Analysis

Overall prevalence of cannabis use was calculated for all mothers in each group, as well as at each time period among those reporting any use. Analyses examined associations of maternal cannabis use in the peri-pregnancy period, pre-conception only (i.e., not in pregnancy), during pregnancy, during each trimester and during breastfeeding, with ASD (vs. DD and vs. POP). Mothers who reported no cannabis use during peri-pregnancy or breastfeeding were the reference group for all analyses. Generalized linear mixed effects models were used for all tests. Given differing legal status and social norms around cannabis in different states, site was included as a random effect in all models. Significance of fixed effects was tested using a type III F-test for fixed effects using Satterthwaite's degrees of freedom. Because prior research suggested an interaction between effects of prenatal cannabis and tobacco use on neurodevelopment of the offspring (Eiden et al., 2018; Stroud et al., 2018), interaction effects were tested using a partial F-test to determine need for stratified analysis. When no interaction effects were observed, peri-pregnancy tobacco use was included as a confounding variable in adjusted models. Maternal education and peri-pregnancy alcohol use were included in all adjusted models based on known associations with prenatal cannabis use (Mark et al, 2016). Children missing information on maternal education or tobacco or alcohol use (N = 16, 0.3%) were excluded. SEED phase, child sex, maternal race/ethnicity and peri-pregnancy use of other illicit drugs were examined as potential confounding variables and retained if effect estimates changed ≥ 10% with their inclusion. R version 3.6.1 (2019-07-05) and the lme4 package v(1.1-21) were used for analysis.

Results

Of 4343 children who completed a clinic visit, the mothers of 4284 (98.6%) responded to cannabis use questions. Mothers of 186 (4.3%) children reported peri-pregnancy cannabis use, while 98 (2.3%) reported use during pregnancy, declining from 2.1% in the first trimester to 0.7% in the second and 0.5% in the third trimester, and 0.6% during breastfeeding. Of mothers reporting no pre-conception cannabis use, 14 (0.3%) used cannabis during pregnancy and 2 (< 0.1%) during breastfeeding. Prevalence of peri-pregnancy cannabis use was similar in all study groups (Table 1), as were observed declines in use from the pre-conception period (Table 2).

In unadjusted analyses, children with ASD were significantly more likely than children in the DD group to have a mother who reported using cannabis during the peri-pregnancy period or only in the 3 months before conception (Table 3). Results were similar in magnitude but not statistically significant for use during pregnancy, in the first trimester or while breastfeeding. In unadjusted analyses, there was no evidence that children with ASD were more likely than POP group children to have mothers who used cannabis during the peri-pregnancy period, only pre-conception, or during pregnancy (Table 3).

As with cannabis use, tobacco use declined from pre-conception to the third trimester (Online Resource 1). There were no significant interactions between self-reported cannabis use and tobacco use during the peri-pregnancy period ($p = 0.70$ for the interaction term when comparing to DD and $p = 0.32$ when comparing to POP), during pre-conception ($p = 0.83$ and $p = 0.23$, respectively), or during pregnancy ($p = 0.35$ and $p = 0.32$, respectively).

Table 1 Characteristics of Participants by Study Group, the Study to Explore Early Development (SEED)

	Autism Spectrum Disorder (ASD) N = 1458	Non-ASD Developmental Delays/ Disorders (DD) N = 1198	General Population (POP) N = 1628
	N (%)	N (%)	N (%)
Any peri-pregnancy[a] cannabis use	76 (5)	38 (3)	72 (4)
Study phase			
SEED 1	687 (47)	677 (57)	879 (54)
SEED 2	771 (53)	521 (43)	749 (46)
Site			
California	226 (16)	203 (17)	260 (16)
Colorado	270 (19)	237 (20)	323 (20)
Georgia	282 (19)	249 (21)	299 (18)
Maryland	253 (17)	159 (13)	248 (15)
North Carolina	225 (15)	217 (18)	274 (17)
Pennsylvania	202 (14)	133 (11)	224 (14)
Child's sex			
Female	268 (18)	419 (35)	774 (48)
Male	1,189 (82)	779 (65)	854 (52)
Maternal Race/Ethnicity			
Hispanic	179 (13)	156 (13)	131 (8)
Non-Hispanic Black	333 (23)	195 (17)	218 (14)
Non-Hispanic White	738 (52)	717 (61)	1124 (70)
Other/Multiracial	169 (12)	102 (9)	137 (9)
Maternal education at time of child's birth			
Less than bachelor's degree	701 (48)	469 (39)	513 (32)
Bachelor's degree or higher	754 (52)	728 (61)	1114 (68)
Household income in 12 months before pregnancy			
Less than $50,000	568 (40)	387 (33)	421 (26)
$50,000 or more	848 (60)	774 (67)	1174 (74)
Ever smoker	556 (38)	406 (34)	552 (34)
Any peri-pregnancy tobacco use	227 (16)	116 (10)	148 (9)
Any peri-pregnancy alcohol use	684 (47)	610 (51)	964 (59)
Any peri-pregnancy use of other illicit drugs[b]	20 (1)	17 (1)	17 (1)
	Mean (SD)	Mean (SD)	Mean (SD)
Child age (in months)	57.2 (8.3)	57.5 (8.7)	56.6 (9.0)

[a]Peri-pregnancy period includes 3 months before pregnancy through the third trimester

[b]Including cocaine, ecstasy, methamphetamines or other illicit drug use

Table 2 Number and percentage of mothers who reported using cannabis in each time period, among mothers who reported any use, Study to Explore Early Development (SEED)

	All N = 186	ASD N = 76	DD N = 38	POP N = 72
Pre-conception[a]	168 (90%)	72 (95%)	36 (95%)	60 (83%)
Pregnancy	98 (53%)	39 (51%)	22 (58%)	37 (51%)
First trimester	90 (48%)	37 (49%)	19 (50%)	34 (47%)
Second trimester	29 (16%)	8 (11%)	6 (16%)	15 (21%)
Third trimester	23 (12%)	8 (11%)	6 (16%)	9 (12%)
While breastfeeding	26 (14%)	8 (11%)	4 (11%)	14 (19%)

[a]During 3 months pre-conception

After adjusting for peri-pregnancy tobacco and alcohol use and maternal education, children with ASD did not differ significantly from children in the DD or POP groups in their likelihood of having a mother who reported using cannabis at any time during the peri-pregnancy period, pre-conception only, or during pregnancy (Table 3). No other variables confounded this relationship. Analyses of cannabis use by trimester and during breastfeeding were based on small numbers of users, precluding covariate adjustment.

Table 3 Odds of self-reported perinatal cannabis use among children with autism spectrum disorder (ASD) compared to children with other developmental delays/disorders (DD) or from the general population (POP), the Study to Explore Early Development (SEED)

Study groups	Time period of cannabis exposure	N	OR (95% CI)	
			Crude[a]	Adjusted[a, b]
ASD vs DD	Peri-pregnancy[c]	2,644	1.71(1.15, 2.54)	1.39 (0.91, 2.11)
	Pre-conception only[d]	2,582	1.91 (1.05, 3.47)	1.58 (0.86, 2.92)
	Pregnancy	2,591	1.52 (0.90, 2.58)	1.21 (0.70, 2.10)
	First trimester	2,586	1.66 (0.95, 2.91)	–[e]
	Second trimester	2,544	1.11 (0.38, 3.21)	–
	Third trimester	2,544	1.11 (0.38, 3.22)	–
	Breastfeeding	2,542	1.71 (0.51, 5.70)	–
ASD vs POP	Peri-pregnancy[c]	3,075	1.19 (0.86, 1.66)	0.89 (0.62, 1.27)
	Pre-conception only[d]	2,994	1.31 (0.81, 2.13)	1.02 (0.61, 1.70)
	Pregnancy	3,003	1.19 (0.75, 1.88)	0.85 (0.52, 1.38)
	First trimester	2,998	1.23 (0.77, 1.97)	–[e]
	Second trimester	2,950	0.60 (0.25, 1.42)	–
	Third trimester	2,944	1.00 (0.39, 2.61)	–
	Breastfeeding	2,949	0.65 (0.27, 1.54)	–

[a]Includes random intercept for site

[b]Adjusted for maternal education, and alcohol and tobacco use during peri-pregnancy

[c]Maternal cannabis use from 3 months prior to conception through the third trimester

[d]Maternal cannabis use during the 3 months prior to conception but not in pregnancy

[e]Analyses by trimester or during breastfeeding were based on small number of users, precluding covariate adjustment

Discussion

In this community-based case–control study of preschool-aged children, we aimed to quantify the association between maternal cannabis use prior to conception and throughout pregnancy with ASD. We found that maternal self-reported use of cannabis in the peri-pregnancy period was not associated with ASD, after accounting for maternal education and peri-pregnancy tobacco and alcohol use. Peri-pregnancy cannabis use was uncommon in this sample of mothers who delivered between 2003 and 2011, when medical use was illegal at some study sites and adult non-medical use was illegal at all sites. However, self-reported prenatal cannabis use has been found to underestimate prevalence measured by positive toxicology by at least 50% (Young-Wolff et al., 2017), hence true prevalence in our sample may have been higher. Most women who reported using cannabis during pregnancy did so only in the first trimester; nearly all were continuing use from the pre-conception period. Mark et al. (2017) found that among women who reported using cannabis at the time of pregnancy diagnosis, 34% continued use in pregnancy, with 96% reporting they did so to treat nausea.

Several longitudinal studies have examined the effect of prenatal cannabis use on neurobehavioral outcomes. Corsi et al. (2020) found that self-reported cannabis use was associated with a significantly increased risk of ASD diagnosis compared to the general population. Differences in SEED sample and methods may help explain our differing results, specifically, a higher prevalence of prenatal cannabis use in our sample, determination of ASD case status by research-reliable clinicians, and inclusion of children not previously diagnosed with ASD (about one-third of cases). Our study expands on Corsi et al.'s findings by comparing children with ASD to those with other neurodevelopmental disorders as well as to population controls and by examining use and risk by trimester and during breastfeeding. Other cohort studies, none of which examined ASD risk, have reported measurable, albeit small and somewhat inconsistent, differences in some facets of cognition and behavior, beginning around 4 years of age (Day et al., 1994; Fried & Watkinson, 1990; Griffith et al., 1994; Metz & Borgelt, 2018; National Academies Press, 2017; Roncero et al., 2020). The endocannabinoid system plays an important role in fetal brain development (Helliwell et al., 2004; Richardson et al., 2016) and cannabinoid receptors are widespread in the fetal cerebral cortex, hippocampus and basal ganglia (Jutras-Aswad et al., 2009). Further, Δ9-tetrahydrocannabinol (THC) and its metabolites are known to freely pass the placental barrier and the fetal blood–brain barrier (Little & VanBeveren, 1996). In rodent studies, prenatal or perinatal exposure to cannabinoids leads to enduring changes in the developing brain (Roncero et al., 2020). Therefore, questions remain about potential harms from prenatal cannabis exposure, including possible effects on ASD risk.

There were limitations to this study. Relatively few mothers reported cannabis use, limiting statistical power to detect associations, to examine adjusted associations with use by trimester or during breastfeeding, and to test interactions with prenatal tobacco use. We excluded mothers who did not answer questions on drug use, which may have introduced selection bias, although only 1% of otherwise eligible participants were excluded for this reason. While self-reported prenatal cannabis use collected 1 year after delivery correlates moderately well with data from antenatal interviews (Jacobson et al., 2002), recall may be less accurate 3–5 years later. Only two SEED sites were in states with legalized medical cannabis use during the period when most interviews were conducted, thus social biases may have contributed to under-reporting in both cases and controls. Self-reported cannabis use during pregnancy has low sensitivity but high specificity compared to serial urine testing (El Marroun et al., 2011; Young-Wolff et al., 2020); exposure misclassification may therefore have biased our findings. We also lacked information about route of ingestion, dose, and frequency of use. In the SEED study, a substantial number of families identified from recruitment sources could not be contacted. Analyses from one SEED site found non-response to be associated with younger maternal age, lower maternal education, and non-white race (Schieve et al., 2018), which have been associated with cannabis use (Ko et al., 2015; Mark et al., 2016). Further, other lifestyle and health-related behaviors of participants who agreed to participate in SEED's intensive research protocol may differ from those not represented in this study. These differences may affect the generalizability of our findings.

This study also has several strengths, including use of research-reliable administration of standardized instruments to evaluate and classify children with ASD, identification and inclusion of children not previously diagnosed with autism (perhaps reflecting lack of care access or milder symptoms), comprehensive data collection enabling examination of multiple covariates known to be associated with cannabis use, and inclusion of two different control groups (Schendel et al., 2012).

With medical and adult non-medical cannabis use currently legal in in most US states and in many other countries, the prevalence of peri-pregnancy use may increase. Given the potential risk suggested by underlying neurobiology and existing animal and epidemiological studies, larger studies with more detailed information on frequency, amount and mode of intake are needed to determine the relationship between cannabis use and ASD and other adverse neurodevelopmental outcomes. The large Generation R Study, an ongoing cohort study from fetal life until adulthood (Kooijman et al., 2016), as well as planned follow-up into adolescence and adulthood of children enrolled in SEED, may provide important new data on this topic. Until more definitive information is available, counseling women regarding potential adverse consequences of cannabis use during pregnancy and lactation and discouraging its use during this period is recommended (ACOG, 2017).

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Declarations

Conflict of interest All authors declare they have no conflict of interest.

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