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Birth and early developmental screening outcomes associated with cannabis exposure during pregnancy

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Abstract

Objective: To compare birth and early developmental screening outcomes for infants with and without *in utero* cannabis exposures.

Study design: Observational cohort of women receiving prenatal care within a large health system, live birth between 10/1/15–12/1/17, and at least one infant visit. Cannabis exposure was through routine urine toxicology screen. Preterm birth, small for gestational age (SGA) birth, birth defects, and early developmental screening outcomes were assessed from birth and electronic health record data.

Results: Of 3435 women, 283 (8.2%) had a positive urine toxicology screen. *In utero* cannabis exposure was associated with SGA birth, adjusted rate ratio (aRR) 1.69 (95% confidence interval [CI]: 1.22–2.34). Abnormal 12-month developmental screens occurred in 9.1% of infants with *in utero* cannabis exposure versus 3.6% of those with negative maternal screens, aRR 1.90 (95% CI: 0.92–3.91). Additional birth outcomes were not associated with *in utero* cannabis exposure.

Conclusion: Exposure to cannabis during pregnancy may adversely impact fetal growth.

Introduction

Access to cannabis continues to increase across North America. As of June 2019, eleven states and the District of Columbia had legalized cannabis for recreational use, and an additional 21 states had legalized medical use of cannabis.(1) In October 2018, Canada became the first large developed nation to legalize cannabis for recreational use.(2) Along with reducing barriers to access, laws legalizing marijuana may also impact public perceptions regarding the risks and benefits of cannabis, including when used during pregnancy.(3) Pregnant women report self-medicating with cannabis to treat nausea, anxiety or pain.(4–6) A 2017 study in Colorado, following marijuana legalization for medical and

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recreational use, found that a majority of cannabis dispensaries in the state recommended cannabis as a treatment for morning sickness.(7)

Data from national surveys suggest that cannabis exposures in pregnancy are on the rise. In a national sample of US adults, between 2002 and 2016, self-reported cannabis use during pregnancy increased from 2.9% to 5%.(8) Others have described that up to 8% of women 18–25 years of age self-report cannabis use in pregnancy.(9) In a recent convenience sample of 306 women from an urban academic obstetric clinic, 35% reported use of marijuana at the time their pregnancy was identified, and approximately one-third of these women reported continued use following their pregnancy diagnosis.(5)

Although research to date on the safety of cannabis use in pregnancy has been inconsistent, these exposures may confer unique effects on fetal growth and development.(10, 11) Delta-9-tetrahydrocannabinol (THC), the active substance in cannabis, can cross the placenta and enter fetal circulation.(12) Prior studies of associations between THC exposure and birth and developmental outcomes have been limited in their ability to control for important confounders such as cigarette use and socioeconomic status.(13) Others have relied on self-report to assess marijuana use and therefore may have underestimated exposures.(14, 15) Few studies to date include longitudinal assessments of infant development following routine, practice-based screening for cannabis exposure during pregnancy.

Given reported trends in prenatal cannabis use, many have called for increased research on birth and developmental outcomes in offspring.(10, 16–18) Among women with one or more prenatal visits and a subsequent live birth within a large Midwestern health system, we aimed to evaluate whether *in utero* exposure to cannabis was associated with adverse birth outcomes, including preterm birth, small-for-gestational age (SGA) birth, low birth weight and major structural birth defects. In addition, among the subset of infants with continued care in our health system for the first year of life, we evaluated the relationship between *in utero* cannabis exposure and abnormal developmental screens at 9 and 12 months of age.

Materials and Methods

We conducted a retrospective observational cohort study, using administrative and electronic health record (EHR) data from women with prenatal care and a subsequent singleton live birth in a large integrated health system primarily in Minnesota, where cannabis is legalized for medical but not for recreational use.

Study population

Our study population included women receiving prenatal care at one of 15 obstetric practices within a single large health system administering routine urine toxicology screening during prenatal visits. Using automated methods, women with a prenatal visit with urine toxicology screening during 7/1/15–3/31/17 were identified from the EHR. We also required that there was a singleton live birth occurring from 10/1/15–12/1/17 and that infants received primary care within the same health system for their first six months of life. Infants with primary care visits were identified through Current Procedural Terminology (CPT)

codes (99381, 99391, 99382, 99392) or International Classification of Diseases, Tenth revision (ICD-10-CM) codes (Z00.110, .111, .121, .129). Infants and mothers were linked through EHR and administrative data. Mothers with multiple gestation pregnancies or non-live birth outcomes were excluded, as were pregnancies that could not be linked to an infant record.

Exposure

Since March 2015, obstetric clinics providing prenatal care within our health system have implemented routine urine toxicology screening for THC and other substances for all pregnant women (amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, oxycodone, phenylcyclidine) at the first prenatal visit, generally between 6 and 14 weeks' gestation. If screening was not conducted at the first visit, it was completed later in the course of prenatal care. Urine specimens were routinely collected at the community-based outpatient obstetrics clinics. Specimens were then transported, processed and tested at a single hospital-based laboratory. The laboratory used SYVA EMIT immunoassay (Siemens Healthineers) with a cutoff of 50 ng/mL to detect 11-nor-9-THC-9-COOH, a THC metabolite, on a Beckman AU680 automated chemistry platform. Positive immunoassays underwent reflex confirmatory testing by gas chromatography-mass spectrometry (GC-MS) selected-ion-monitoring (SIM). Urine creatinine was also tested and the urine toxicology screen was deemed invalid if the urine creatinine was <20 mg/dl. In cases where urine toxicology screens were repeated in the same pregnancy, exposure status was based on the results of the first urine THC screen.

Outcomes

Preterm birth: We applied a standard definition of delivery before 37 weeks gestation to signify preterm birth. Gestational age at delivery was identified through infant birth records and were based on clinical assessment at birth.

Low birth weight and Small for gestational age birth: Birth weights were obtained from infant birth records and from the EHR. Low birth weight was defined as <2500g. We assigned weight for gestational age percentiles based on reference values derived by Oken et al.(19) As in our prior work, a cut-off of <10th percentile was used to classify a birth as small for gestational age (SGA).(20, 21)

Major structural birth defects: Major structural birth defects were identified based on selected ICD-10-CM diagnostic codes from infant outpatient visits or as noted on the problem list. The list of major structural defects was adapted from prior work by our group, (22, 23) with codes updated from ICD-9-CM to ICD-10-CM using a crosswalk developed by the Centers for Disease Control and Prevention Birth Defects Branch for use in the National Birth Defects Prevention Network.(24) In order to reduce the likelihood of capturing diagnostic workups for a defect that either was not confirmed or miscoded, we required infants have 2 or more outpatient diagnoses or that the defect was noted in the problem list. A list of ICD-10 codes used to identify major structural birth defects is found in Appendix 1. Given the availability of head circumference measurements and the potential for prenatal cannabis exposures to impact neurodevelopment(10), potential cases of congenital

microcephaly were identified through the ICD-10 code (Q02) and then confirmed through review of head circumference measurements at birth and at outpatient follow-up, standardized based on intergrowth-21st references by gestational age at birth. Congenital microcephaly was defined as head circumference <3rd percentile at birth and persistent at outpatient follow-up, after excluding secondary causes for microcephaly.

Screen positive for developmental delay: Parent completed developmental screening questionnaires(25) are routinely administered as part of well-baby check-ups within our health system, with results stored in retrievable discrete flowsheets in the EHR. The Ages and Stages Questionnaire III (ASQ-3) screens early communication and motor skills, problem-solving and personal-social skills. The Ages and Stages: Social-Emotional Questionnaire (ASQ-SE) is a brief survey of important social-emotional domains in infancy and early childhood, including self-regulation, compliance, communication, adaptive behaviors, autonomy, affect and interaction with people. In this study we utilized results from the ASQ-3 recorded at 9 months and the ASQ-SE administered at 12 months. For the 9-month ASQ-3, we applied standard published cut-offs by area: Communication <13.97, Gross motor <17.82, Fine motor <31.32, Problem solving <28.72 and Personal-social <18.91.(26) For the 12-month ASQ-SE, consistent with published definitions, a score of >50 indicated an abnormal screen.(27) Reliability of these tools is strong (for the ASQ-3: 0.93 interrater reliability; 0.92 test-retest reliability,(28) 75% sensitivity and 81% specificity;(29) for the ASQ-SE: 0.94 test-retest reliability, 71% sensitivity and 97% specificity at 12 months).(27)

Covariates

We collected data on maternal sociodemographic and clinical factors associated with either likelihood or marijuana exposures, increased risk for adverse birth or developmental outcomes, or both. These were identified from the EHR and included: age, race/ethnicity, insurance, pre-pregnancy body mass index, use of folic acid, opioid or other drug use as identified on their first trimester urine toxicology screen, and smoking during pregnancy. Maternal comorbidities occurring prior to pregnancy including hypertension, diabetes, sickle cell disease, lupus and other rheumatologic disorders were also evaluated as potential risks for preterm and SGA births. Maternal neurologic disorders including seizures were evaluated as women with these disorders may be more likely to have a medical prescription for marijuana. Use of interpreter services was also reviewed, given the potential for parental proficiency in English to impact results of infant developmental screening.

Analyses

We conducted descriptive analyses of sociodemographic variables. Two potential sources of bias in constructing the cohort were evaluated. First we compared rates of having a positive THC screen in women whose pregnancies linked to a live birth versus those whose pregnancies did not link to a live birth. Second, we compared distributions of baseline characteristics by THC screening results. Frequency distributions and means with standard deviation were reported, and statistical significance ($p < 0.05$) was evaluated with chi-square or t-test, accordingly. To evaluate the association between THC exposure and adverse birth and developmental outcomes, frequency of events by THC screening results were estimated,

and unadjusted and adjusted rate ratios (RR)s with 95% confidence intervals (CI)s were estimated using generalized linear models. The model used a Poisson distribution with log link and robust variance estimation. Covariates included in the models were smoking during pregnancy, age, pre-pregnancy body mass index, and race/ethnicity. In addition, for infant developmental outcomes, gestational age was included in the model. Given the strong association between smoking and birth weight, in secondary analyses, the association between THC exposure and SGA is stratified by maternal smoking.

In preparation for conducting this study, we prepared a power analysis. With a minimum sample of 4,000 mother-infant pairs, an expected 5% THC exposure during first trimester and 80% power, with $\alpha=.05$, we would be powered to detect a RR of 2.7 for major birth defects or an abnormal developmental screen, based on a background prevalence rate of 2 per 100 live births. We would be powered to detect a RR of 1.8 for preterm or SGA birth, both with a background rate of 8 per 100 live births.

This study was approved by the HealthPartners Institutional Review Board with a waiver of informed consent.

Results

Of 8,592 women with a prenatal visit at one of 15 obstetric clinics within a single health system during 7/1/15–3/31/17, 4,500 (52%) were linked to a live born infant. Of these, 3,435 (76%) remained eligible, undergoing urine toxicology screening during pregnancy, having a singleton infant with care in the health system following birth. (Figure 1) Among pregnant women linked to a live birth, 94% had a THC screen completed, and 8.2% were positive. A majority (69%) of urine THC screening was conducted between 6 and 14 weeks gestation. Women who did not have a THC screen recorded during pregnancy did not differ in baseline characteristics from those who completed the screening (data available upon request.) For women without linkage to a live birth, 89% had a THC screen completed and 11% were positive.

As compared to women with a negative THC screen in pregnancy, women with a positive screen were significantly younger (mean age 25.4 versus 29.9 years), more likely to be non-Hispanic Black (39.6% versus 23.2%), have public insurance (53.0% versus 27.1%) and report smoking cigarettes during pregnancy (41.7% versus 5.9%). Interpreter use at one or more infant visits occurred for 7.7% of women with negative THC screens versus none of the women with positive THC screens. Other covariates, including parity, folic acid use, pre-pregnancy body mass index, alcohol use, additional results of first trimester urine toxicology screens, and maternal comorbidities prior to pregnancy did not differ significantly between women with positive and negative urine THC screens. (Table 1)

Preterm birth, before 37 weeks gestation, occurred in 169 (5.4%) women with a negative THC screen versus 20 (7.1%) women with a positive THC screen. In adjusted analyses, these differences were not significant, with an adjusted RR (aRR) of 1.06 (95% CI: 0.64–1.77). An SGA birth, <10th percentile, occurred in 290 (9.4%) infants born to women with a negative THC screen versus 53 (19.0%) infants born to women with a positive THC screen.

In analyses adjusting for maternal race/ethnicity, pre-pregnancy body mass index, age and smoking during pregnancy, having a positive urine THC screen was significantly associated with having an SGA birth, with an aRR of 1.69 (95% CI: 1.22–2.34). In secondary analyses of SGA and THC exposure, stratified by maternal smoking, the aRR was 1.42 (95% CI: 0.93–2.15) in women who did not smoke cigarettes and 2.38 (95% CI: 1.35–4.19) in women who reported smoking cigarettes during pregnancy. Major structural birth defects, including microcephaly, were rare in both groups and were not significantly associated with in utero THC exposures, aRR of 0.58 (95% CI: 0.17–2.00). (Table 2)

Of the full cohort with birth outcome data, 68.7% with a negative THC screen and 54.1% with a positive THC screen had 9-month ASQ-3 developmental screens completed. For the 12-month ASQ-SE developmental screens, retention rates were 57.7% among those with a negative THC screen and 46.6% among those with a positive THC screen. (Figure 1) In unadjusted and adjusted analyses, scoring below published thresholds on the ASQ-3 9-month screen was not associated with THC exposure. For the 12-month ASQ-SE screen, abnormal or above the published screening threshold was noted in 9.1% of infants born to a mother with a positive THC screen versus 3.6% of those born to a mother with a negative THC screen. After adjusting for race/ethnicity, age, and smoking during pregnancy, these differences were not statistically significant, aRR 1.90 (95% CI: 0.92–3.91). (Table 2)

Discussion

The American College of Obstetrics and Gynecology (ACOG) encourages women who are pregnant or contemplating pregnancy to discontinue use of cannabis.(30) Findings from our observational study of over 3,000 women, including 283 with a positive THC screen in pregnancy, support these recommendations. We observed that cannabis exposure in pregnancy was relatively common and associated with a 70% increased risk of SGA birth. In addition, we observed a trend towards increased risk for abnormal developmental screening at 12 months of age among infants with *in utero* cannabis exposures, although the findings were not statistically significant in adjusted analyses.

One challenge in interpreting observational studies of cannabis exposures during pregnancy is how to address potential confounders or factors that may differ between cannabis users and non-users. In our study, 42% of women with positive urine THC screens also self-reported smoking cigarettes during pregnancy. In contrast, less than 6% of women with negative THC screens smoked cigarettes. In analyses stratified by smoking status, the effect of THC on SGA birth was highest in women who also reported cigarette use. Other factors that differed significantly at baseline and could also be associated with SGA birth included maternal age and maternal race/ethnicity.

Overall, prior studies on the associations between maternal cannabis use and birth outcomes have applied varied exposure definitions, and have produced conflicting results. One recent systematic review and meta-analysis published in 2016, reported that maternal cannabis use was associated with decreased birth weight and increased risk for admission to a neonatal intensive care unit.(31) However, a second systematic review and meta-analysis, published in the same year, reported that after adjusting for tobacco exposures, cannabis use in

pregnancy was not associated with increased risk for preterm birth or low birth weight.(13) In a combined analysis of data from three longitudinal cohorts, cannabis use alone was associated with lower birth weight and co-use of cannabis and tobacco was not associated with additional risks.(32) Two recent large population-based studies from Canada have found prenatal cannabis exposures were associated with preterm and SGA birth.(33, 34) In contrast, in the current study we found maternal cannabis exposure was positively associated with SGA birth, but not associated with low birth weight or preterm birth.

Prior studies of cannabis use in pregnancy and developmental outcomes in children have more consistently demonstrated harm. In a study of 648 children, maternal self-report of heavy cannabis use in first trimester was associated with lower verbal reasoning scores and heavy use in second trimester was associated with deficits in short-term memory.(35) By age 10, prenatal cannabis exposures have been associated with increased hyperactivity, impulsivity and inattention by parent report and increased teacher reported delinquency.(36) We observed a trend towards a positive association between cannabis exposure early in pregnancy and having an abnormal ASQ-SE at 12 months of age, although results were not significant in adjusted analyses. Our cohort retention at 12 months of age was approximately 57%, with increased loss to follow-up among mothers with positive THC screens in pregnancy. With a background rate of abnormal 12-month ASQ-SE screening of 3 to 4%, we were underpowered to detect even a 2-fold increase associated with maternal cannabis use. As the validity of the ASQ-SE to detect true social-emotional difficulty increases with the child's age at screening(27) continued monitoring of development with a larger cohort and over a longer follow-up period is needed.

The findings we report should also be considered in the context of limitations in our measurement tools. The ASQ-3 and ASQ-SE are commonly used in pediatric primary care practice for identifying infants and young children at risk for developmental delays and socioemotional difficulties. However, these are parent-report surveys and not diagnostic tools. The ASQ-3 and ASQ-SE have been used in prior studies of neurodevelopment following prenatal exposures.(37, 38) Nevertheless, at this early age these developmental screens may not be optimally sensitive to the types of cognitive and self-regulatory difficulties detected through formal neurocognitive assessments later in childhood following *in utero* cannabis exposures. Future investigations should include formal neurocognitive assessments, including measurement of emerging executive function skills, to fully evaluate potential detrimental effects of prenatal cannabis exposures as described in prior studies.(11)

A number of mechanisms have been proposed as potential pathways for THC to impact embryologic and fetal development, including through the reduction of folic acid, inhibition of vascular endothelial growth factor, induction of apoptosis, and inhibition of cell migration.(39) THC is stored in fat deposits in maternal and fetal tissue. The typical half-life for THC is 8 days; frequent users may have THC detected in blood or urine up to 30 days after last use. Although the majority of urine toxicology screening was conducted between 6 and 14 weeks gestation, there was heterogeneity in the timing of screening, limiting our ability to identify risks by timing of cannabis exposure in pregnancy. Furthermore, given the sample size, we were not able to compare women with a single positive screen versus those with continued cannabis use during pregnancy. In addition, we were not able to assess the

cannabis exposure dose or route. The risks associated with cannabis exposure may be increased when cannabis is smoked as compared to ingested, as combustion releases numerous potentially harmful toxins and carcinogens.(40)

Our study was also underpowered to detect associations between individual major structural birth defects and maternal cannabis use, as background prevalence rates for individual defects are in the range of 1–10 per 10,000 births. As such, we applied a composite outcome of any pre-specified major structural defect and found no association with prenatal cannabis exposure. Also, there was potential for misclassification of exposure status. Women with an initial negative urine THC screen are generally not screened again later in pregnancy yet exposures may occur, potentially biasing results to the null. Finally, we were only able to capture results of developmental screening for a subset of the full cohort undergoing maternal urine toxicology screening and those with positive THC screens were more likely to be lost to follow-up at 9 and 12 months.

Despite these limitations, the current study provides timely and needed data on the prevalence and potential risks of maternal cannabis use during pregnancy among women receiving care in a community-based integrated health system. Additional studies with larger cohorts, longer follow-up, and more extensive neurodevelopmental screening are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ASQ-3	Ages and Stages Questionnaire III
ASQ-SE	Ages and Stages Questionnaire: Social-Emotional
CI	Confidence interval
EHR	Electronic health record
ICD-10-CM	International Classification of Diseases – 10 th Revision
SGA	Small for gestational age

THC Delta-9-tetrahydrocannabinol

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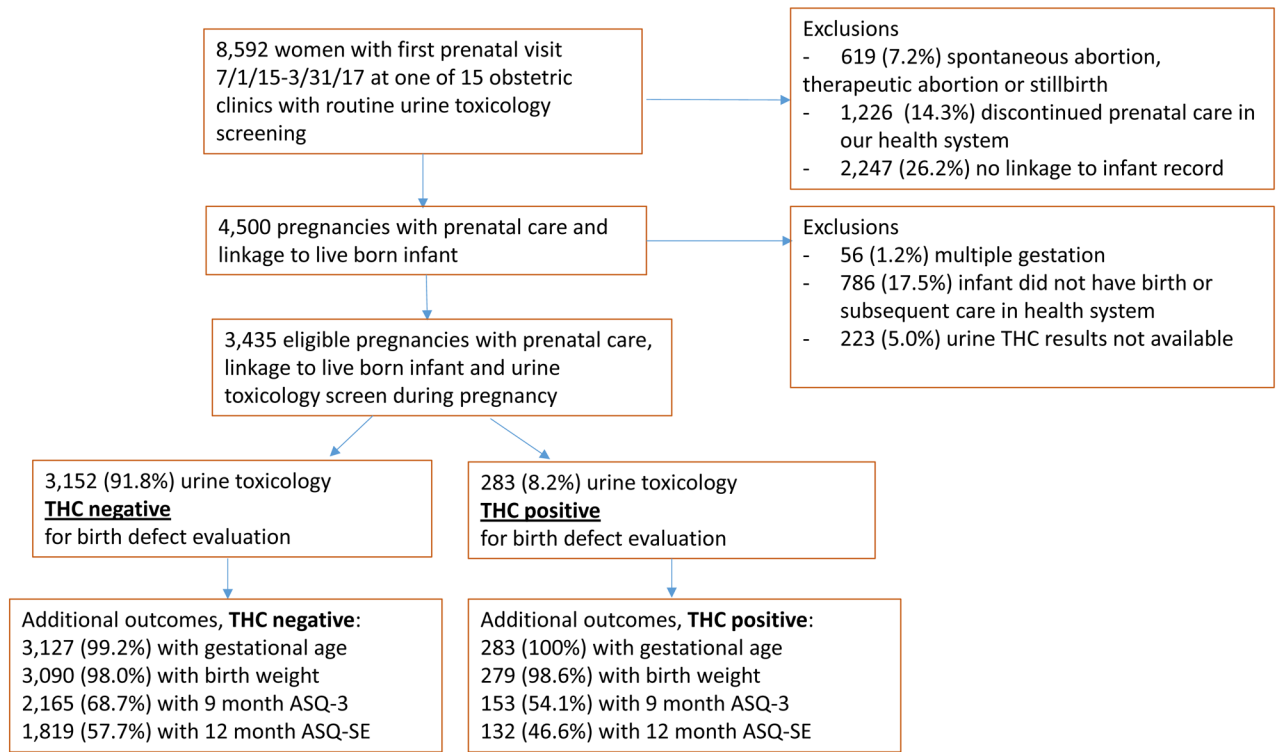


Figure 1. Identification of cohort, inclusions and exclusions

THC = Tetrahydrocannabinol;

ASQ-3 = Ages and Stages Questionnaire III;

ASQ-SE = Ages and Stages Questionnaire, Social-Emotional

Table 1.

Baseline characteristics of women by urine tetrahydrocannabinol (THC) exposure in pregnancy

		THC negative n=3152	THC positive n=283
Maternal age in years *	Mean (SD)	29.9 (5.0)	25.4 (5.3)
Maternal race/ethnicity *	N (%)		
Non-Hispanic Asian		489 (15.5)	2 (<1)
Non-Hispanic African American		732 (23.2)	112 (39.6)
Hispanic		140 (4.4)	20 (7.1)
Non-Hispanic White		1578 (50.1)	121 (42.8)
Other or not available		213 (6.8)	28 (9.9)
Body mass index (kg/m ²)	Mean (SD)	27.5 (6.4)	28.1 (7.2)
Number of live births	Mean (SD)	2.1 (1.3)	1.9 (1.1)
Interpreter use at infant visits *	N (%)	243 (7.7)	0 (0)
Medicaid *	N (%)	853 (27.1)	150 (53.0)
Folic acid use in pregnancy [†]	N (%)	2861 (90.8)	265 (93.6)
Smoking during pregnancy *	N (%)	186 (5.9)	118 (41.7)
Self-report alcohol prior 12 months	N (%)	1008 (32.0)	93 (32.9)
Urine toxicology screen completed between 6–14 weeks gestation	N (%)	2192 (70.1)	188 (66.4)
Positive opioid urine toxicology	N (%)	17 (0.5)	4 (1.4)
Other positive urine toxicology ^{‡‡}	N (%)	28 (0.9)	6 (2.1)
Pre-existing comorbidities ^{‡‡‡}	N (%)	121 (3.8)	16 (5.7)

THC = Tetrahydrocannabinol;

[†]Folic acid use based on active medication list in electronic health record;^{‡‡}Other positive urine toxicology includes amphetamines, cocaine, phenylcyclidine, benzodiazepines, barbiturates^{‡‡‡}Pre-existing maternal comorbidities include: epilepsy and other neurologic disorders, diabetes, hypertension, sickle cell disease and other hematologic disorders, lupus and other rheumatologic disorders. Conditions identified through problem lists and diagnoses in 6 months prior to last menstrual period;

* Differences between THC positive and THC negative in pregnancy significant at p<.0001

Table 2.

Birth and developmental screening outcomes by urine tetrahydrocannabinol (THC) exposure, with and without adjustment

	THC negative		THC positive		Unadjusted	Adjusted****
	n	n (%)	n	n (%)	RR (95% CI)	RR (95% CI)
Preterm birth <37 weeks gestation	3127	169 (5.4)	283	20 (7.1)	1.31 (0.83–2.05)	1.06 (0.64–1.77)
Low birth weight <2500g	3090	114 (3.7)	279	23 (8.2)	2.23 (1.44–3.47)	1.27 (0.86–1.86)
Small for gestational age <10 th percentile	3090	290 (9.4)	279	53 (19.0)	2.02 (1.53–2.67)	1.69 (1.22–2.34)
Major structural birth defect*	3152	52 (1.6)	283	3 (1.1)	0.65 (0.20–2.06)	0.58 (0.17–2.00)
ASQ-SE 12-month Abnormal**	1819	66 (3.6)	132	12 (9.1)	2.51 (1.37–4.58)	1.90 (0.92–3.91)
ASQ-3 9-month Subscale Below Cutoff***						
Communication	2168	35 (1.6)	153	2 (1.3)	0.81 (0.20–3.33)	1.08 (0.27–4.26)
Gross Motor	2167	86 (4.0)	153	5 (3.3)	0.82 (0.34–1.99)	0.92 (0.35–2.41)
Fine Motor	2168	532 (24.5)	153	26 (17.0)	0.69 (0.49–0.98)	0.91 (0.63–1.31)
Problem Solving	2166	174 (8.0)	153	12 (7.8)	0.98 (0.56–1.71)	1.39 (0.75–2.57)
Personal-Social	2165	133 (6.1)	153	6 (3.9)	0.64 (0.29–1.41)	0.79 (0.34–1.85)

THC = Tetrahydrocannabinol; ASQ-3 = Ages and Stages Questionnaire III; ASQ-SE: Ages and Stages Questionnaire: Social-Emotional; RR = Rate ratio

* Defined as having 2 or more diagnoses in first year of life or defect noted in problem list;

For full list of birth defects, please see Appendix A

** ASQ-SE 12-month abnormal defined as above 50

*** ASQ-3 9-month Communication Subscale Cutoff=13.97; ASQ-3 9-month Gross Motor Subscale Cutoff=17.82; ASQ-3 9-month Fine Motor Subscale Cutoff=31.21; ASQ-3 9-month Problem Solving Subscale Cutoff=28.72; ASQ-3 9-month Personal-Social Subscale Cutoff=18.91;

**** Rate ratios for preterm birth, SGA birth and major structural birth defects adjusted for maternal race/ethnicity, maternal age, body mass index, and smoking during pregnancy; rate ratios for ASQ-3 and ASQ-SE results also adjusted for gestational age at birth.