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Prenatal Marijuana Exposure and Neonatal Outcomes

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ABSTRACT

Objectives: Previous literature on the effects of marijuana exposure on neonatal outcomes has been limited by the reliance on maternal self-report. The objective of this study was to examine the relationship of prenatal marijuana exposure on neonatal outcomes in infants with marijuana exposure confirmed with meconium drug testing.

Design: Retrospective cohort study.

Setting and participants: Meconium drug screens obtained on infants born in a hospital system in the Pacific Northwest in the United States over a 2.5-year period. 1804 meconium drug screens were initially obtained, with 1540 drug screens included in the analysis.

Primary and secondary outcome measures: Neonates with meconium drug screens positive for delta-9-tetrahydrocannabinol (THC) only were compared to neonates with negative drug screens. The following neonatal outcomes were examined: gestational age, preterm birth (<37 weeks), birth weight, low birth weight (defined as birth weight < 2.5 kg), length, head circumference, Apgar scores and admission to the Neonatal Intensive Care Unit (NICU). Using multivariable logistical and linear regression we controlled for confounding variables.

Results: 1540 meconium drug screens were included in the analysis, with 483 positive for delta-9-tetrahydrocannabinol (THC) only. Neonates exposed to delta-9-tetrahydrocannabinol (THC) had significantly lower birth weight, head circumference and length ($p<0.001$). Neonates with THC exposure had 1.9 times the odds (95% CI: 1.3-2.7, $p=0.001$) of being defined as low birth weight. Birth weight was on average 0.16 kg lower (95% CI: 0.10 to 0.22, $p<0.001$) in those exposed to THC.

Conclusions: Prenatal marijuana exposure was significantly associated with decreases in birth weight, length, and head circumference, and an increased risk of being defined as low birth weight. These findings add to the previous literature demonstrating possible negative effects of prenatal marijuana use on neonatal outcomes.

Strengths and limitations of this study

- We used biochemical data to define THC use which decreased the probability of under-reporting of marijuana use during pregnancy.
- We controlled for important confounders that have limited previous research on this subject.
- We excluded meconium drug screens with substances other than THC, eliminating the effect of polysubstance abuse.
- We evaluated tobacco and alcohol use through self-report rather than through biochemical data.

INTRODUCTION

Marijuana is frequently used in pregnancy with increasing prevalence of use over the past ten years.[1] In the 2018 National Survey on Drug Use and Health, 4.7% of pregnant women aged 15-44 years and 9.8% of pregnant women aged 18-25 years used marijuana in the previous month.[1] Complicating the issue is data suggesting that the self-report of marijuana use may underestimate the actual prevalence.[2-4] Both the American Academy of Pediatrics (AAP) and the American College of Obstetrics and Gynecology (ACOG) have policy statements recommending against marijuana use during pregnancy.[5,6] Despite public health campaigns, there remains a large proportion of pregnant women who perceive marijuana use as without risk.[7] This discussion is particularly important with studies showing increased use of marijuana in states with legalization.[8]

Previous literature examining the effect of marijuana on neonatal outcomes is varied.[9,10] A 2016 metanalysis by Gunn et al, found a decrease in birth weight and higher neonatal intensive care unit (NICU) admission rates in infants exposed to marijuana.[9] One limitation of this metanalysis was many of the studies did not control for or exclude individuals with polysubstance use, including alcohol and tobacco, which limited the ability to examine the independent effect of marijuana.[9] In addition, many of the studies relied on the self-report of marijuana rather than on biochemical samples.[9] A separate metanalysis by Conner et al, did control for tobacco and polysubstance drug use.[10] In the unadjusted analysis, marijuana use was associated with lower birth weight, and preterm birth.[10] However, in the adjusted analysis, when controlling for concomitant tobacco use, marijuana use was not found to be associated with low birth weight or preterm birth.[10] One of the limitations of this metanalysis was that 20 of the 31 included studies determined marijuana exposure by self-report alone.[10] Meconium drug screens are an objective

way to evaluate drug exposure and have traditionally been considered the gold standard for detection.[11] Meconium screens are thought to primarily reflect second and third trimester drug exposure and are therefore most useful in assessing drug use in the later portion of pregnancy.[11,12]

With the background of this varied literature, the objective of this current study was to examine the effect of prenatal marijuana exposure on the following neonatal outcomes: gestational age, preterm birth (<37 weeks), birth weight, low birth weight (defined as < 2.5 kg), length, head circumference, Apgar scores and admission to the NICU.

METHODS

Design, setting and participants

This was a retrospective cohort study using an electronic medical record with individual chart review from 01/01/2017 through 06/20/2019 for a complete hospital network in the Pacific Northwest. Recreational use of marijuana was legal during the entire study timeframe. Inclusion criteria included all cases with meconium drug screens recorded. Cases were excluded if any other drug (other than delta-9- tetrahydrocannabinol (THC)) was detected in meconium and in charts with significant missing data. Meconium drug screens are routinely obtained on infants within the hospital system based on the following criteria: no prenatal care, less than 5 prenatal visits, prenatal care initiated at 20 weeks or later, documented or admitted drug use by the mother or spouse within 2 years, mother in drug rehabilitation program or infant exhibiting drug withdrawal. Meconium drug screens evaluated for the presence of the following: methamphetamine, amphetamines, barbiturates, cocaine, opiates, oxycodone, phencyclidine, methadone, propoxyphene, and benzodiazepines. Alcohol and tobacco use was evaluated from maternal self-report through routine prenatal visit questionnaires. The timing and amount of

exposure to alcohol and tobacco was not specifically evaluated. The study received exempt status from the hospital system's institutional review board.

Outcomes

The primary predictor was prenatal exposure to marijuana as defined by a positive meconium test for THC. Covariates collected included maternal age, race/ethnicity, self-reported alcohol/tobacco use, cervical insufficiency, multiple gestation, maternal diabetes and hypertension. Outcomes included gestational age, preterm birth, NICU admission, low birth weight (defined as less than 2.5 kg), birth weight, length, head circumference and Apgar scores. To examine the bivariate association between rates of preterm birth and NICU admission with prenatal marijuana exposure, we performed chi-square tests. To determine if there was an adjusted difference in birth weight, height and head circumferences between those with versus without prenatal marijuana exposure, we used two-sample t-tests. Given the previous criticism of studies that did not consider important confounders [9], we controlled for important maternal and gestational factors using multivariable regression analysis. For the dichotomous outcomes of preterm birth and NICU admission, we utilized multivariable logistic regression. For the continuous outcomes of birth weight, length and head circumferences, we utilized multivariable linear regression.

Patient and public involvement

Patients or the public were not involved in the design, conduct, or reporting of this study.

RESULTS

Population characteristics

There were 1,804 patients for which a meconium sample was screened, 101 (5.6%) of which were excluded for significant missing data (Figure 1). There were a total of 11,617 births in the

hospital network during the study period, therefore close to 15% of all newborns had a meconium drug screen obtained. For the primary analysis we excluded patients whose sample contained any substances in addition to/other than THC (163, 9.6%), leading to a final sample size of 1,540.

THC was detected in 483 (31.3%) of meconium samples. Within this cohort, patients who tested positive for THC were more likely to be Caucasian, use tobacco and less likely to have diabetes (Table 1).

Table 1. Patient characteristics, comorbidities, and risk factors by THC status, N=1540

	Overall, N=1,540	**THC positive, n=483**	**No substance, n=1,057**
Patient characteristics			
Maternal age, mean(sd)	27.2(5.6)	26.5(5.1)	27.6(5.7)
Race and ethnicity, n(%)			
White	1231(79.9%)	408(84.5%)	823(77.9%)
Black	47(3.1%)	16(3.3%)	31(2.9%)
Hispanic	115(7.5%)	22(4.6%)	93(8.8%)
Other/Unknown	147(9.6%)	37(7.7%)	110(10.4%)
Comorbidities & Risk Factors			
Tobacco use, n(%)	612(39.7%)	214(44.3%)	398(37.7%)
Alcohol use, n(%)	35(2.3%)	12(2.5%)	23(2.2%)
Diabetes, n(%)	211(13.7%)	53(11%)	158(15%)
Hypertension, n(%)	289(18.8%)	84(17.4%)	205(19.4%)
Cervical insufficiency, n(%)	19(1.2%)	4(0.8%)	15(1.4%)
Multiple gestation, n(%)	41(2.7%)	11(2.3%)	30(2.8%)

In unadjusted analyses, neonates who tested positive for THC had significantly lower birth weight, shorter length and smaller head circumference (p<0.001) (Table 2).

Table 2: Unadjusted outcomes by THC status, n=1,540

Outcomes	**Overall, N=1,540**	**THC positive, n=483**	**No substance, n=1,057**	**p-value***
Gestational age (weeks), mean(sd)	38.9(2.0)	38.9(1.7)	38.9(2.1)	0.651
Preterm birth (<37 weeks), n(%)	152(9.9%)	44(9.1%)	108(10.2%)	0.499
NICU admission, n(%)	189(12.3%)	56(11.6%)	133(12.6%)	0.583
Length (cm), mean(sd)	**50.1(3.1)**	**49.5(2.9)**	**50.3(3.2)**	**<0.001**
Weight (kg), mean(sd)	**3.25(0.58)**	**3.13(0.56)**	**3.31(0.59)**	**<0.001**
Low birth weight (<2.5kg), n(%)	**136(8.8%)**	**59(12.2%)**	**77(7.3%)**	**0.002**
Head Circumference (cm), mean(sd)	**34(2.2)**	**33.6(2.5)**	**34.2(2)**	**<0.001**
5-minute Apgar, mean(sd)	8.7(0.7)	8.8(0.7)	8.7(0.7)	0.333

*t-tests for continuous data; chi-square tests for categorical data

Marijuana exposed neonates were also more likely to be designated as low birth weight (<2.5kg).

Adjusted analysis

In the adjusted analysis, neonates exposed to THC had significantly lower birth weight, shorter length and smaller head circumference (p<0.001) (Table 3).

Table 3. Results from adjusted linear regression analyses, n=1,539

Model Covariates	**Birth weight** Regression Coefficient (95% CI)	**P-value**	**Head circumference** Regression Coefficient (95% CI)	**p-value**	**Length** Regression Coefficient (95% CI)	**p-value**
THC positive	***-0.16(-0.22 to -0.10)***	***<0.001***	***-0.52(-0.78 to -0.27)***	***<0.001***	***-0.71(-1.03 to -0.39)***	***<0.001***
Patient characteristics						
Maternal age	***0.01(0.00 to 0.01)***	***0.032***	***0.02(0.01 to 0.04)***	***0.009***	0.02(-0.01 to 0.05)	0.159
Race/ethnicity						
White	referent	0.449	referent	0.861	referent	0.212
Black	-0.04(-0.21 to 0.12)		-0.01(-0.88 to 0.85)		-0.51(-1.65 to 0.62)	
Hispanic	-0.04(-0.15 to 0.07)		-0.09(-0.48 to 0.30)		-0.30(-0.99 to 0.40)	
Other/Unknown	0.06(-0.04 to 0.16)		-0.16(-0.56 to 0.25)		0.42(-0.09 to 0.93)	
Comorbidities & Risk Factors						
Tobacco use	***-0.15(-0.21 to -0.09)***	***<0.001***	***-0.41(-0.64 to -0.17)***	***0.001***	***-0.79(-1.12 to -0.46)***	***<0.001***
Alcohol use	-0.12(-0.31 to 0.07)	0.228	-0.78(-2.01 to 0.45)	0.214	-0.56(-1.48 to 0.36)	0.232
Diabetes	0.03(-0.05 to 0.11)	0.462	-0.01(-0.33 to 0.32)	0.957	0.14(-0.32 to 0.59)	0.550
Hypertension	***-0.18(-0.25 to -0.10)***	***<0.001***	***-0.36(-0.62 to -0.10)***	***0.008***	***-0.72(-1.14 to -0.29)***	***0.001***
Cervical insufficiency	-0.18(-0.43 to 0.08)	0.173	-0.48(-1.53 to 0.56)	0.362	-1.61(-3.52 to 0.30)	0.099
Multiple gestation	***-0.66(-0.84 to -0.49)***	***<0.001***	***-1.47(-2.13 to -0.81)***	***<0.001***	***-3.48(-4.49 to -2.47)***	***<0.001***

Multivariable linear regression controlled for tobacco use, alcohol use, diabetes, hypertension, cervical insufficiency, and multiple gestation.
Note: there was one patient missing age and was excluded from multiple regression models.

Birth weight was on average 0.16 kg lower (95% CI: 0.10 to 0.22, p<0.001) in those exposed to THC. Head circumference was on average 0.52 cm lower (95% CI: 0.27 to 0.78, p<0.001) in those exposed to THC. Length was on average 0.71 cm lower (95% CI: 0.39 to 1.03, p<0.001) in those exposed to THC. As compared to those unexposed to THC, those exposed had 1.9 times the odds (95% CI: 1.3-2.7, p=0.001) of being defined as low birth weight in the adjusted analysis (Table 4).

Table 4. Results from adjusted logistic regression analyses, n=1,539

Model Covariates	Preterm birth OR (95% CI)	P-value	NICU admission OR (95% CI)	p-value	Low birth weight OR (95% CI)	p-value
THC positive	0.9(0.6-1.3)	0.685	0.9(0.7-1.3)	0.67	***1.9(1.3-2.7)***	***0.001***
Patient characteristics						
Maternal age	1.0(1.0-1.0)	0.626	1.0(1.0-1.0)	0.194	1.0(1.0-1.0)	0.960
Comorbidities & Risk Factors						
Tobacco use	***1.7(1.2-2.4)***	***0.002***	***1.9(1.4-2.6)***	***<0.001***	***1.8(1.2-2.6)***	***0.002***
Alcohol use	0.8(0.2-2.7)	0.724	1.0 (0.4-2.6)	0.993	1.2(0.4-3.4)	0.792
Diabetes	***1.6(1.0-2.5)***	***0.038***	1.3(0.9-2.0)	0.195	1.6(1.0-2.6)	0.054
Hypertension	1.2(0.8-1.8)	0.510	1.6(1.1-2.3)	0.014	***1.6(1.0-2.4)***	***0.033***
Cervical insufficiency	***3.0 (1.0-8.8)***	***0.047***	1.3(0.4-4.5)	0.725	2.9(0.9-9.2)	0.072
Multiple gestation	***6.0 (3.1-11.7)***	***<0.001***	***4.0 (2.0-7.9)***	***<0.001***	***5.7(2.8-11.4)***	***<0.001***

Multivariable logistic regression controlled for tobacco use, alcohol use, diabetes, hypertension, cervical insufficiency, and multiple gestation.
Note: there was one patient missing age and was excluded from multiple regression models.

There were no significant associations between THC exposure and preterm birth or NICU admission. Although not included in our adjusted model, there was no significant association between THC exposure and Apgar scores. We were not able to include race in the multivariable analysis of dichotomous outcomes due to insufficient sample size. In preliminary adjusted logistic regression analyses, the p-value for race was >0.60 for all dichotomous outcomes and thus was chosen for removal.

We used robust standard errors for the analyses of head circumference and length due to evidence of heteroskedasticity of the residuals. All models were tested for multicollinearity which was not present. All other regression diagnostics indicated good model fit.

DISCUSSION

This study found that prenatal marijuana exposure was significantly associated with decreased birth weight, length and head circumference. In addition, infants exposed to marijuana were more likely to be defined as low birth weight compared to those unexposed.

Similar to many previous studies, our data showed a decreased birth weight in infants exposed to marijuana.[3,9,13-16] On average, the birth weight in infants exposed to marijuana in our cohort was 160 grams lower than in those unexposed and exposed infants were more likely to be classified as low birth weight. This finding is similar to previously published work demonstrating a higher incidence of low birth weight infants exposed to marijuana.[15,17,18] These findings are particularly relevant in terms of newborn care as it relates to the increased need for blood work and testing.[19] Increased newborn blood draws can be associated with breastfeeding disruption, hyperalgesia, and parental anxiety, underscoring the importance in ameliorating factors such as THC use that may contribute to lower birth weight.[20,21]

Our study further demonstrated a decreased birth length in infants exposed to marijuana. Previous studies evaluating this outcome have been contradictory.[3,14,16,22-24] In our cohort, infants exposed to marijuana were also more likely to have a decreased birth head circumference. Similarly, previous work evaluating this outcome has been conflicting.[3,14,16,22-25] The finding of decreased head circumference in the exposed group is potentially multifactorial. Previous studies have linked maternal alcohol use with decreased head circumference.[26] Given that alcohol use was self-reported, and potentially under reported, in our population, one could hypothesize that the decreased head circumference could be partially related to alcohol use.

Previous literature evaluating the effect of marijuana exposure on NICU admission is also inconsistent. Similar to previously reported data, our study did not show an increased risk of

NICU admission in infants exposed to marijuana.[3,10,17] This is in contrast to research demonstrating an increased risk of NICU admission in infants exposed to marijuana.[13,15,18] Our study is also similar to previous literature which did not show an association with marijuana exposure and preterm birth.[9,10,13,17,27] In contrast, other studies have shown an association with marijuana exposure and preterm birth.[15,28-30] Lastly, although not included in our adjusted model, our study did not show a significant difference in the five minutes Apgar scores for THC exposed infants, which is consistent with previously reported studies.[3,14,23,24,31,32]

Our study used a potentially higher risk initial population due to the inclusion criteria for obtaining a meconium drug screen. However, both the study group (THC positive meconium) and comparison group (THC negative meconium) were derived from this initial population of infants that had a meconium collected. Meconium drug screens that were positive for drugs other than THC were excluded from the analysis. Therefore, the comparison group consisted of infants with completely negative meconium drug screens. The authors intentionally did not derive a comparison group from infants who did not have meconium collected given the concern that this may have introduced significant bias between the study and comparison group.

The etiology of discrepant findings of marijuana exposure on neonatal outcomes is likely multifaceted. Previous authors have hypothesized that the strong reliance on self-report of marijuana use could bias studies toward the null hypothesis by misclassifying marijuana users as non-users.[3] To our knowledge, our study is one of the largest in the United States ever to examine the effects of marijuana on neonates using targeted drug screen results, rather than maternal self-report.[9,10] As previously noted, in the metanalysis by Conner et al, 20 of the 31 studies included relied on maternal self-report of marijuana use.[3,10] Unlike the Gunn et al metanalysis, which included many studies that did not control for tobacco use, our study

rigorously controlled for potential confounders such as tobacco use, increasing the ability to evaluate for the independent effect of marijuana on neonatal outcomes.[9] This ability to control for important confounders, large sample size, use of biochemical data to define THC use, and the exclusion of polysubstance use may explain some of the differences found in our study compared to previous literature. Our findings underscore the importance in continued adherence to both AAP and ACOG guidelines which recommend counseling women against using marijuana during pregnancy. Our research adds to the growing literature demonstrating potential negative effects of marijuana use during pregnancy and highlights the need for continued national conversations regarding its widespread use.

There are many limitations to our study. The retrospective cohort design inherently limits the ability to determine causality. Second, there was lack of racial diversity in the cohort possibly limiting generalizability. Third, we unable to access the precise reason for a meconium screen being obtained other the general category of reasons previously enumerated, which may have introduced unmeasured confounders. Fourth, both alcohol and tobacco use were self-reported which may have resulted in the underreporting of exposure. Fifth, we may have introduced selection bias by only examining neonates who had meconium drug screens. However, it could be hypothesized that if we had compared neonates without meconium drug screens, we may have found even greater differences. Future prospective studies could ameliorate this possible bias by studying cohorts that employ universal drug testing. Sixth, as meconium screens primarily detect second and third trimester drug exposure, we did not evaluate early pregnancy drug use. Finally, we did not quantify marijuana exposure in our population which would have allowed for more granular interpretation and analysis.

CONCLUSIONS

To our knowledge, our study is one of the largest in the United States ever to examine the effects of marijuana on neonates using targeted drug testing results rather than maternal self-report. In our study, prenatal marijuana exposure was significantly associated with decreased birth weight, length, head circumference and risk of being low-birth weight after controlling for important confounders. These findings highlight the need for continued education of pregnant women and adherence to both AAP and ACOG guidelines in avoiding marijuana use in pregnancy.

Contributor Statements:

Dr. Jones conceptualized and designed the study, interpreted the data, drafted the initial manuscript, and approved the final manuscript as submitted.

Dr. Lotfi collected the initial data, interpreted the data, revised the manuscript, and approved the final manuscript as submitted.

Ms. Lin carried out the initial data analyses, interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Dr. Gievers, Dr. Hendrickson, and Dr. Sheridan reviewed and interpreted the data, revised the manuscript, and approved the final manuscript as submitted.

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Patient consent for publication: Not applicable.

Ethics approval: The study received exempt status from the hospital system's institutional review board.

Data availability: Data are available upon reasonable request.

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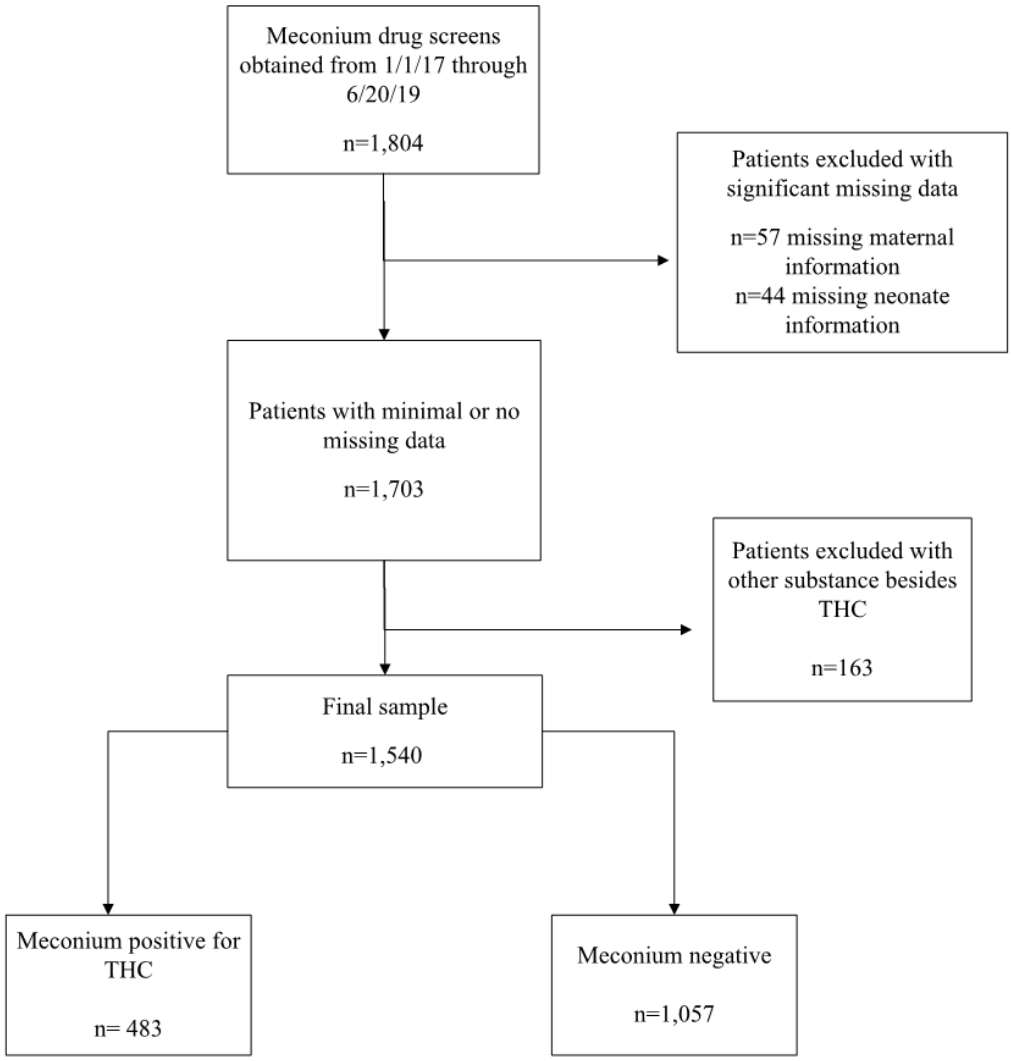
Figure 1: Flowchart for study cohort



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	(a) 8 (b) 8 (c)8-9 (d)n/a (e)n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	(a)8-9 (b)8-9 (c)appendix
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	(a)8-9 (b)8-9
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(a)10-12 (b)11-12 (c)n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Prenatal Marijuana Exposure and Neonatal Outcomes: A Retrospective Cohort Study

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- Marijuana
- Pregnancy
- THC
- Prenatal substance use
- Adverse neonatal outcomes

ABSTRACT

Objectives: Previous literature on the effects of marijuana exposure on neonatal outcomes has been limited by the reliance on maternal self-report. The objective of this study was to examine the relationship of prenatal marijuana exposure on neonatal outcomes in infants with marijuana exposure confirmed with meconium drug testing.

Design: Retrospective cohort study.

Setting and participants: Meconium drug screens obtained on infants born in a hospital system in the Pacific Northwest in the United States over a 2.5-year period. 1804 meconium drug screens were initially obtained, with 1540 drug screens included in the analysis.

Primary and secondary outcome measures: Neonates with meconium drug screens positive for delta-9-tetrahydrocannabinol (THC) only were compared to neonates with negative drug screens. The following neonatal outcomes were examined: gestational age, preterm birth (<37 weeks), birth weight, low birth weight (defined as birth weight < 2.5 kg), length, head circumference, Apgar scores and admission to the Neonatal Intensive Care Unit (NICU). Using multivariable logistical and linear regression we controlled for confounding variables.

Results: 1540 meconium drug screens were included in the analysis, with 483 positive for delta-9-tetrahydrocannabinol (THC) only. Neonates exposed to delta-9-tetrahydrocannabinol (THC) had significantly lower birth weight, head circumference and length ($p<0.001$). Neonates with THC exposure had 1.9 times the odds (95% CI: 1.3-2.7, $p=0.001$) of being defined as low birth weight. Birth weight was on average 0.16 kg lower (95% CI: 0.10 to 0.22, $p<0.001$) in those exposed to THC.

Conclusions: Prenatal marijuana exposure was significantly associated with decreases in birth weight, length, and head circumference, and an increased risk of being defined as low birth weight. These findings add to the previous literature demonstrating possible negative effects of prenatal marijuana use on neonatal outcomes.

Strengths and limitations of this study

- We used biochemical data to define THC use which decreased the probability of under-reporting of marijuana use during pregnancy.
- We controlled for important confounders that have limited previous research on this subject.
- We excluded meconium drug screens with substances other than THC, eliminating the effect of polysubstance abuse.
- We evaluated tobacco and alcohol use through self-report rather than through biochemical data.

INTRODUCTION

Marijuana is frequently used in pregnancy with increasing prevalence of use over the past ten years.[1] In the 2018 National Survey on Drug Use and Health, 4.7% of pregnant women aged 15-44 years and 9.8% of pregnant women aged 18-25 years used marijuana in the previous month.[1] Complicating the issue is data suggesting that the self-report of marijuana use may underestimate the actual prevalence.[2-4] Both the American Academy of Pediatrics (AAP) and the American College of Obstetrics and Gynecology (ACOG) have policy statements recommending against marijuana use during pregnancy.[5,6] In addition, the Centers for Disease Control and Prevention (CDC) and the Surgeon General recommend not using marijuana during pregnancy.[7,8] Despite public health campaigns, there remains a large proportion of pregnant women who perceive marijuana use as without risk.[9] This discussion is particularly important with studies showing increased use of marijuana in states with legalization.[10]

Previous literature examining the effect of marijuana on neonatal outcomes is varied.[11,12] A 2016 metanalysis by Gunn et al, found a decrease in birth weight and higher neonatal intensive care unit (NICU) admission rates in infants exposed to marijuana.[11] One limitation of this metanalysis was many of the studies did not control for or exclude individuals with polysubstance use, including alcohol and tobacco, which limited the ability to examine the independent effect of marijuana.[11] In addition, many of the studies relied on the self-report of marijuana rather than on biochemical samples.[11] A separate metanalysis by Conner et al, did control for tobacco and polysubstance drug use.[12] In the unadjusted analysis, marijuana use was associated with lower birth weight, and preterm birth.[12] However, in the adjusted analysis, when controlling for concomitant tobacco use, marijuana use was not found to be associated with low birth weight or preterm birth.[12] One of the limitations of this metanalysis

was that 20 of the 31 included studies determined marijuana exposure by self-report alone.[12] Meconium drug screens are an objective way to evaluate drug exposure and have traditionally been considered the gold standard for detection.[13] Meconium screens are thought to primarily reflect second and third trimester drug exposure and are therefore most useful in assessing drug use in the later portion of pregnancy.[13,14]

With the background of this varied literature, the objective of this current study was to examine the effect of prenatal marijuana exposure on the following neonatal outcomes: gestational age, preterm birth (<37 weeks), birth weight, low birth weight (defined as < 2.5 kg), length, head circumference, Apgar scores and admission to the NICU.

METHODS

Design, setting and participants

This was a retrospective cohort study using an electronic medical record with individual chart review from 01/01/2017 through 06/20/2019 for a complete hospital network in the Pacific Northwest. Recreational use of marijuana was legal during the entire study timeframe. Inclusion criteria included all cases with meconium drug screens recorded. Cases were excluded if any other drug (other than delta-9- tetrahydrocannabinol (THC)) was detected in meconium and in charts with significant missing data. Meconium drug screens evaluated for the presence of the following: methamphetamine, amphetamines, barbiturates, cocaine, opiates, oxycodone, phencyclidine, methadone, propoxyphene, and benzodiazepines. Meconium drug screen tests used a homogeneous enzyme immunoassay method for analysis. The presumptive positive screens were reflexed to mass spectroscopy (MS) methodology. Meconium drug screens are routinely obtained on infants within the hospital system based on the following criteria: no prenatal care, less than 5 prenatal visits, prenatal care initiated at 20 weeks or later, documented

or admitted drug use by the mother or spouse within 2 years, mother in drug rehabilitation program or infant exhibiting drug withdrawal. Alcohol and tobacco use was evaluated from maternal self-report through routine prenatal visit questionnaires. The timing and amount of exposure to alcohol and tobacco was not specifically evaluated. The study received exempt status from the hospital system's institutional review board.

Outcomes

The primary predictor was prenatal exposure to marijuana as defined by a positive meconium test for THC. Covariates collected included maternal age, race/ethnicity, self-reported alcohol/tobacco use, cervical insufficiency, multiple gestation, maternal diabetes and hypertension. Outcomes included gestational age, preterm birth, NICU admission, low birth weight (defined as less than 2.5 kg), birth weight, length, head circumference and Apgar scores. To examine the bivariate association between rates of preterm birth and NICU admission with prenatal marijuana exposure, we performed chi-square tests. To determine if there was an adjusted difference in birth weight, height and head circumferences between those with versus without prenatal marijuana exposure, we used two-sample t-tests. To control for type I error, we calculated p-values using the Benjamini and Hochberg false discovery rate correction. For outcomes with a significant ($p<0.05$) bivariate association with THC, we conducted multivariable regression analyses to control for important maternal and gestational factors, including tobacco use, alcohol use, diabetes, hypertension, cervical insufficiency, and multiple gestation. For the dichotomous outcome of preterm birth, we utilized multivariable logistic regression. For the continuous outcomes of birth weight, length and head circumferences, we utilized multivariable linear regression.

Patient and public involvement:

Patients or the public were not involved in the design, conduct, or reporting of this study.

RESULTS

Population characteristics

There were 1,804 patients for which a meconium sample was screened, 101 (5.6%) of which were excluded for significant missing data (Figure 1). There were a total of 11,617 births in the hospital network during the study period, therefore close to 15% of all newborns had a meconium drug screen obtained. For the primary analysis we excluded patients whose sample contained any substances in addition to/other than THC (163, 9.6%) (supplement), leading to a final sample size of 1,540. THC was detected in 483 (31.3%) of meconium samples. Within this cohort, patients who tested positive for THC were more likely to be Caucasian, use tobacco and less likely to have diabetes (Table 1).

Table 1. Patient characteristics, comorbidities, and risk factors by THC status, N=1540

	Overall, N=1,540	**THC positive, n=483**	**No substance, n=1,057**
Patient characteristics			
Maternal age, mean(sd)	27.2(5.6)	26.5(5.1)	27.6(5.7)
Race and ethnicity, n(%)			
White	1231(79.9%)	408(84.5%)	823(77.9%)
Black	47(3.1%)	16(3.3%)	31(2.9%)
Hispanic	115(7.5%)	22(4.6%)	93(8.8%)
Other/Unknown	147(9.6%)	37(7.7%)	110(10.4%)
Comorbidities & Risk Factors			
Tobacco use, n(%)	612(39.7%)	214(44.3%)	398(37.7%)
Alcohol use, n(%)	35(2.3%)	12(2.5%)	23(2.2%)
Diabetes, n(%)	211(13.7%)	53(11%)	158(15%)
Hypertension, n(%)	289(18.8%)	84(17.4%)	205(19.4%)
Cervical insufficiency, n(%)	19(1.2%)	4(0.8%)	15(1.4%)
Multiple gestation, n(%)	41(2.7%)	11(2.3%)	30(2.8%)

In unadjusted analyses, neonates who tested positive for THC had significantly lower birth weight, shorter length and smaller head circumference (p<0.003) (Table 2).

Table 2: Unadjusted outcomes by THC status, n=1,540

Outcomes	**Overall, N=1,540**	**THC positive, n=483**	**No substance, n=1,057**	**p-value***
Gestational age (weeks), mean(sd)	38.9(2.0)	38.9(1.7)	38.9(2.1)	0.651
Preterm birth (<37 weeks), n(%)	152(9.9%)	44(9.1%)	108(10.2%)	0.651
NICU admission, n(%)	189(12.3%)	56(11.6%)	133(12.6%)	0.651
Length (cm), mean(sd)	**50.1(3.1)**	**49.5(2.9)**	**50.3(3.2)**	**0.003**
Weight (kg), mean(sd)	**3.25(0.58)**	**3.13(0.56)**	**3.31(0.59)**	**0.003**
Low birth weight (<2.5kg), n(%)	**136(8.8%)**	**59(12.2%)**	**77(7.3%)**	**0.004**
Head Circumference (cm), mean(sd)	**34(2.2)**	**33.6(2.5)**	**34.2(2)**	**0.003**
5-minute Apgar, mean(sd)	8.7(0.7)	8.8(0.7)	8.7(0.7)	0.533

*t-tests for continuous data; chi-square tests for categorical data; reported p-values are corrected for multiple testing using the Benjamini and Hochberg false discovery rate correction

Marijuana exposed neonates were also more likely to be designated as low birth weight (<2.5kg).

Adjusted analysis

In the adjusted analysis, neonates exposed to THC had significantly lower birth weight, shorter length and smaller head circumference (p<0.001) (Table 3).

Table 3. Results from adjusted linear regression analyses, n=1,539

Model Covariates	**Birth weight** Regression Coefficient (95% CI)	**P-value**	**Head circumference** Regression Coefficient (95% CI)	**p-value**	**Length** Regression Coefficient (95% CI)	**p-value**
THC positive	***-0.16(-0.22 to -0.10)***	***<0.001***	***-0.52(-0.78 to -0.27)***	***<0.001***	***-0.71(-1.03 to -0.39)***	***<0.001***
Patient characteristics						
Maternal age	***0.01(0.00 to 0.01)***	***0.032***	***0.02(0.01 to 0.04)***	***0.009***	0.02(-0.01 to 0.05)	0.159
Race/ethnicity						
White	referent	0.449	referent	0.861	referent	0.212
Black	-0.04(-0.21 to 0.12)		-0.01(-0.88 to 0.85)		-0.51(-1.65 to 0.62)	
Hispanic	-0.04(-0.15 to 0.07)		-0.09(-0.48 to 0.30)		-0.30(-0.99 to 0.40)	
Other/Unknown	0.06(-0.04 to 0.16)		-0.16(-0.56 to 0.25)		0.42(-0.09 to 0.93)	
Comorbidities & Risk Factors						
Tobacco use	***-0.15(-0.21 to -0.09)***	***<0.001***	***-0.41(-0.64 to -0.17)***	***0.001***	***-0.79(-1.12 to -0.46)***	***<0.001***
Alcohol use	-0.12(-0.31 to 0.07)	0.228	-0.78(-2.01 to 0.45)	0.214	-0.56(-1.48 to 0.36)	0.232
Diabetes	0.03(-0.05 to 0.11)	0.462	-0.01(-0.33 to 0.32)	0.957	0.14(-0.32 to 0.59)	0.550
Hypertension	***-0.18(-0.25 to -0.10)***	***<0.001***	***-0.36(-0.62 to -0.10)***	***0.008***	***-0.72(-1.14 to -0.29)***	***0.001***
Cervical insufficiency	-0.18(-0.43 to 0.08)	0.173	-0.48(-1.53 to 0.56)	0.362	-1.61(-3.52 to 0.30)	0.099
Multiple gestation	***-0.66(-0.84 to -0.49)***	***<0.001***	***-1.47(-2.13 to -0.81)***	***<0.001***	***-3.48(-4.49 to -2.47)***	***<0.001***

Multivariable linear regression controlled for tobacco use, alcohol use, diabetes, hypertension, cervical insufficiency, and multiple gestation.
Note: there was one patient missing age and was excluded from multiple regression models

Birth weight was on average 0.16 kg lower (95% CI: 0.10 to 0.22, p<0.001) in those exposed to THC. Head circumference was on average 0.52 cm lower (95% CI: 0.27 to 0.78, p<0.001) in those exposed to THC. Length was on average 0.71 cm lower (95% CI: 0.39 to 1.03, p<0.001) in those exposed to THC. As compared to those unexposed to THC, those exposed had 1.9 times the odds (95% CI: 1.3-2.7, p=0.001) of being defined as low birth weight in the adjusted analysis (Table 4).

Table 4. Results from adjusted logistic regression analyses, n=1,539

Model Covariates	Low birth weight OR (95% CI)	p-value
THC positive	***1.9(1.3-2.7)***	***0.001***
Patient characteristics		
Maternal age	1.0(1.0-1.0)	0.960
Comorbidities & Risk Factors		
Tobacco use	***1.8(1.2-2.6)***	***0.002***
Alcohol use	1.2(0.4-3.4)	0.792
Diabetes	1.6(1.0-2.6)	0.054
Hypertension	***1.6(1.0-2.4)***	***0.033***
Cervical insufficiency	2.9(0.9-9.2)	0.072
Multiple gestation	***5.7(2.8-11.4)***	***<0.001***

Multivariable logistic regression controlled for tobacco use, alcohol use, diabetes, hypertension, cervical insufficiency, and multiple gestation.
Note: there was one patient missing age and was excluded from multiple regression models.

There were no significant association between THC exposure and preterm birth, NICU admission, and Apgar scores. We were not able to include race in the multivariable analysis of dichotomous outcomes due to insufficient sample size. In preliminary adjusted logistic regression analyses, the p-value for race was >0.60 for all dichotomous outcomes and thus was chosen for removal.

We used robust standard errors for the analyses of head circumference and length due to evidence of heteroskedasticity of the residuals. All models were tested for multicollinearity which was not present. All other regression diagnostics indicated good model fit.

DISCUSSION

This study found that prenatal marijuana exposure was significantly associated with decreased birth weight, length and head circumference. In addition, infants exposed to marijuana were more likely to be defined as low birth weight compared to those unexposed.

Similar to many previous studies, our data showed a decreased birth weight in infants exposed to marijuana.[3,11,15-18] On average, the birth weight in infants exposed to marijuana in our cohort was 160 grams lower than in those unexposed and exposed infants were more likely to be classified as low birth weight. This finding is similar to previously published work demonstrating a higher incidence of low birth weight infants exposed to marijuana.[17,19,20] These findings are particularly relevant in terms of newborn care as it relates to the increased need for blood work and testing.[21] Increased newborn blood draws can be associated with breastfeeding disruption, hyperalgesia, and parental anxiety, underscoring the importance in ameliorating factors such as THC use that may contribute to lower birth weight.[22,23]

Our study further demonstrated a decreased birth length in infants exposed to marijuana. Previous studies evaluating this outcome have been contradictory.[3,6,18,24-26] In our cohort, infants exposed to marijuana were also more likely to have a decreased birth head circumference. Similarly, previous work evaluating this outcome has been conflicting.[3,6,18,24-27] The finding of decreased head circumference in the exposed group is potentially multifactorial. Previous studies have linked maternal alcohol use with decreased head circumference.[28]

Given that alcohol use was self-reported, and potentially under reported, in our population, one could hypothesize that the decreased head circumference could be partially related to alcohol use.

Previous literature evaluating the effect of marijuana exposure on NICU admission is also inconsistent. Similar to previously reported data, our study did not show an increased risk of NICU admission in infants exposed to marijuana.[3,12,19] This is in contrast to research demonstrating an increased risk of NICU admission in infants exposed to marijuana.[15,17,20] Our study is also similar to previous literature which did not show an association with marijuana exposure and preterm birth.[11,12,15,19,29] In contrast, other studies have shown an association with marijuana exposure and preterm birth.[30-32] Lastly, our study did not show a significant difference in the five minutes Apgar scores for THC exposed infants, which is consistent with previously reported studies.[3,16,25,26,33,34]

Our study used a potentially higher risk initial population due to the inclusion criteria for obtaining a meconium drug screen. However, both the study group (THC positive meconium) and comparison group (THC negative meconium) were derived from this initial population of infants that had a meconium collected. Meconium drug screens that were positive for drugs other than THC were excluded from the analysis. Therefore, the comparison group consisted of infants with completely negative meconium drug screens. The authors intentionally did not derive a comparison group from infants who did not have meconium collected given the concern that this may have introduced significant bias between the study and comparison group.

The etiology of discrepant findings of marijuana exposure on neonatal outcomes is likely multifaceted. Previous authors have hypothesized that the strong reliance on self-report of marijuana use could bias studies toward the null hypothesis by misclassifying marijuana users as

non-users.[3] To our knowledge, our study is one of the largest in the United States ever to examine the effects of marijuana on neonates using targeted drug screen results, rather than maternal self-report.[11,12] As previously noted, in the metanalysis by Conner et al, 20 of the 31 studies included relied on maternal self-report of marijuana use.[3,12] Unlike the Gunn et al metanalysis, which included many studies that did not control for tobacco use, our study rigorously controlled for potential confounders such as tobacco use, increasing the ability to evaluate for the independent effect of marijuana on neonatal outcomes.[11] This ability to control for important confounders, large sample size, use of biochemical data to define THC use, and the exclusion of polysubstance use may explain some of the differences found in our study compared to previous literature. Our findings underscore the importance in continued adherence to both AAP and ACOG guidelines which recommend counseling women against using marijuana during pregnancy. Our research adds to the growing literature demonstrating potential negative effects of marijuana use during pregnancy and highlights the need for continued national conversations regarding its widespread use.

There are many limitations to our study. The retrospective cohort design inherently limits the ability to determine causality. Second, there was lack of racial diversity in the cohort and we were unable to include race in the multivariable analysis, possibly limiting generalizability. Third, we were unable to assess the precise reason for a meconium screen being obtained other the general category of reasons previously enumerated, which may have introduced unmeasured confounders. Fourth, both alcohol and tobacco use were self-reported which may have resulted in the underreporting of exposure. Fifth, we may have introduced selection bias by only examining neonates who had meconium drug screens rather than utilizing a cohort with universal testing. However, it could be hypothesized that if we had compared neonates without meconium

drug screens, we may have found even greater differences. Future prospective studies could ameliorate this possible bias by studying cohorts that employ universal drug testing. Sixth, as meconium screens primarily detect second and third trimester drug exposure, we did not evaluate early pregnancy drug use. Seventh, there was no separation of maternal hypertensive disorders or maternal type of diabetes. Eighth, there was no exclusion of anomalous fetuses or those with genetic disorders which may have introduced confounding. Ninth, we did not exclude mothers taking medications associated with low birth weight or exclude mothers with autoimmune conditions which may have also introduced confounding. Finally, we did not quantify marijuana exposure in our population which would have allowed for more granular interpretation and analysis.

CONCLUSIONS

To our knowledge, our study is one of the largest in the United States ever to examine the effects of marijuana on neonates using targeted drug testing results rather than maternal self-report. In our study, prenatal marijuana exposure was significantly associated with decreased birth weight, length, head circumference and risk of being low-birth weight after controlling for important confounders. These findings highlight the need for continued education of pregnant women and adherence to both AAP and ACOG guidelines in avoiding marijuana use in pregnancy.

Contributor Statements:

Dr. Jones conceptualized and designed the study, interpreted the data, drafted the initial manuscript, and approved the final manuscript as submitted.

Dr. Lotfi collected the initial data, interpreted the data, revised the manuscript, and approved the final manuscript as submitted.

Ms. Lin carried out the initial data analyses, interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Dr. Gievers, Dr. Hendrickson, and Dr. Sheridan reviewed and interpreted the data, revised the manuscript, and approved the final manuscript as submitted.

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Data availability: Data are available upon reasonable request.

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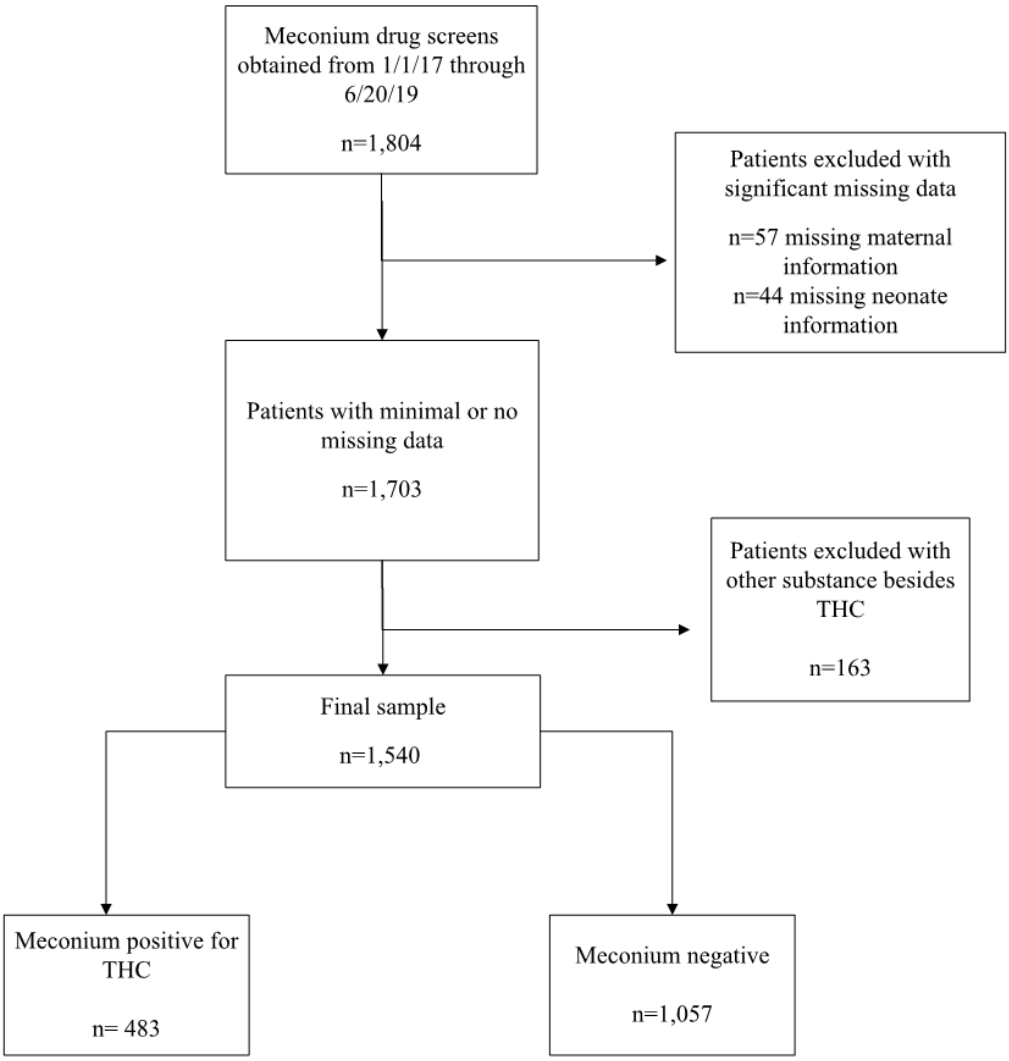
Figure Legend/Caption

Figure 1: Flowchart for Study Cohort. Inclusion criteria included all cases with meconium drug screens recorded. Cases were excluded if any other drug (other than delta-9-tetrahydrocannabinol (THC)) was detected in meconium and in charts with significant missing data.

Figure 1: Flowchart for study cohort



Presence of other drugs in meconium screen by THC status, n=1,703

	All patients, n=1,703	**THC negative, N=1,175**	**THC positive N=528**	**p-value**
Presence of one or more drugs (besides THC) in meconium screen, n(%)	163(9.6%)	118(10.0%)	45(8.5%)	0.324
Presence of drugs in meconium screen, n(%)				
Methamphetamines	84(4.9%)	60(5.1%)	24(4.6%)	0.621
Amphetamines	102(6.0%)	72(6.1%)	30(5.7%)	0.720
Barbiturates	1(0.1%)	1(0.1%)	0(0.0%)	0.503
Cocaine	4(0.2%)	2(0.2%)	2(0.4%)	0.411
Opiates	51(3.0%)	38(3.2%)	13(2.5%)	0.387
Oxycodone	6(0.4%)	4(0.3%)	2(0.4%)	0.902
Phencyclidine	0(0.0%)	0(0.0%)	0(0.0%)	NA
Methadone	29(1.7%)	24(2.0%)	5(1.0%)	0.106
Propoxyphene	0(0.0%)	0(0.0%)	0(0.0%)	NA
Benzodiazepines	0(0.0%)	0(0.0%)	0(0.0%)	NA

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	(a) 8 (b) 8 (c)8-9 (d)n/a (e)n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	(a)8-9 (b)8-9 (c)appendix
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	(a)8-9 (b)8-9
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(a)10-12 (b)11-12 (c)n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Prenatal Marijuana Exposure and Neonatal Outcomes: A Retrospective Cohort Study

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- Marijuana
- Pregnancy
- THC
- Prenatal substance use
- Adverse neonatal outcomes

ABSTRACT

Objectives: Previous literature on the effects of marijuana exposure on neonatal outcomes has been limited by the reliance on maternal self-report. The objective of this study was to examine the relationship of prenatal marijuana exposure on neonatal outcomes in infants with marijuana exposure confirmed with meconium drug testing.

Design: Retrospective cohort study.

Setting and participants: Meconium drug screens obtained on infants born in a hospital system in the Pacific Northwest in the United States over a 2.5-year period. 1804 meconium drug screens were initially obtained, with 1540 drug screens included in the analysis.

Primary and secondary outcome measures: Neonates with meconium drug screens positive for delta-9-tetrahydrocannabinol (THC) only were compared to neonates with negative drug screens. The following neonatal outcomes were examined: gestational age, preterm birth (<37 weeks), birth weight, low birth weight (defined as birth weight < 2.5 kg), length, head circumference, Apgar scores and admission to the Neonatal Intensive Care Unit (NICU). Using multivariable logistical and linear regression we controlled for confounding variables.

Results: 1540 meconium drug screens were included in the analysis, with 483 positive for delta-9-tetrahydrocannabinol (THC) only. Neonates exposed to delta-9-tetrahydrocannabinol (THC) had significantly lower birth weight, head circumference and length ($p<0.001$). Neonates with THC exposure had 1.9 times the odds (95% CI: 1.3-2.7, $p=0.001$) of being defined as low birth weight. Birth weight was on average 0.16 kg lower (95% CI: 0.10 to 0.22, $p<0.001$) in those exposed to THC.

Conclusions: Prenatal marijuana exposure was significantly associated with decreases in birth weight, length, and head circumference, and an increased risk of being defined as low birth weight. These findings add to the previous literature demonstrating possible negative effects of prenatal marijuana use on neonatal outcomes.

Strengths and limitations of this study

- We used biochemical data to define THC use which decreased the probability of under-reporting of marijuana use during pregnancy.
- We controlled for important confounders that have limited previous research on this subject.
- We excluded meconium drug screens with substances other than THC, eliminating the effect of polysubstance abuse.
- We evaluated tobacco and alcohol use through self-report rather than through biochemical data.

INTRODUCTION

Marijuana is frequently used in pregnancy with increasing prevalence of use over the past ten years.[1] In the 2018 National Survey on Drug Use and Health, 4.7% of pregnant women aged 15-44 years and 9.8% of pregnant women aged 18-25 years used marijuana in the previous month.[1] Complicating the issue is data suggesting that the self-report of marijuana use may underestimate the actual prevalence.[2-4] Both the American Academy of Pediatrics (AAP) and the American College of Obstetrics and Gynecology (ACOG) have policy statements recommending against marijuana use during pregnancy.[5,6] In addition, the Centers for Disease Control and Prevention (CDC) and the Surgeon General recommend not using marijuana during pregnancy.[7,8] Despite public health campaigns, there remains a large proportion of pregnant women who perceive marijuana use as without risk.[9] This discussion is particularly important with studies showing increased use of marijuana in states with legalization.[10]

Previous literature examining the effect of marijuana on neonatal outcomes is varied.[11,12] A 2016 metanalysis by Gunn et al, found a decrease in birth weight and higher neonatal intensive care unit (NICU) admission rates in infants exposed to marijuana.[11] One limitation of this metanalysis was many of the studies did not control for or exclude individuals with polysubstance use, including alcohol and tobacco, which limited the ability to examine the independent effect of marijuana.[11] In addition, many of the studies relied on the self-report of marijuana rather than on biochemical samples.[11] A separate metanalysis by Conner et al, did control for tobacco and polysubstance drug use.[12] In the unadjusted analysis, marijuana use was associated with lower birth weight, and preterm birth.[12] However, in the adjusted analysis, when controlling for concomitant tobacco use, marijuana use was not found to be associated with low birth weight or preterm birth.[12] One of the limitations of this metanalysis

was that 20 of the 31 included studies determined marijuana exposure by self-report alone.[12] Meconium drug screens are an objective way to evaluate drug exposure and have traditionally been considered the gold standard for detection.[13] Meconium screens are thought to primarily reflect second and third trimester drug exposure and are therefore most useful in assessing drug use in the later portion of pregnancy.[13,14]

With the background of this varied literature, the objective of this current study was to examine the effect of prenatal marijuana exposure on the following neonatal outcomes: gestational age, preterm birth (<37 weeks), birth weight, low birth weight (defined as < 2.5 kg), length, head circumference, Apgar scores and admission to the NICU.

METHODS

Design, setting and participants

This was a retrospective cohort study using an electronic medical record with individual chart review from 01/01/2017 through 06/20/2019 for a complete hospital network in the Pacific Northwest. Recreational use of marijuana was legal during the entire study timeframe. Inclusion criteria included all cases with meconium drug screens recorded. Cases were excluded if any other drug (other than delta-9- tetrahydrocannabinol (THC)) was detected in meconium and in charts with significant missing data. Meconium drug screens evaluated for the presence of the following: methamphetamine, amphetamines, barbiturates, cocaine, opiates, oxycodone, phencyclidine, methadone, propoxyphene, and benzodiazepines. Meconium drug screen tests used a homogeneous enzyme immunoassay method for analysis. Initial positive screens were reflexed to mass spectroscopy (MS) methodology. Test results were reported as positive if equal to or greater than threshold and negative if below threshold.[15] This test was developed, and its analytical performance characteristics were determined by Quest Diagnostics Nichols Institute

Chantilly, VA.[15] Validation was pursuant to the CLIA (Clinical Laboratory Improvement Amendments) regulations and the test is used for clinical purposes.[15]

Meconium drug screens are routinely obtained on infants within the hospital system based on the following criteria: no prenatal care, less than 5 prenatal visits, prenatal care initiated at 20 weeks or later, documented or admitted drug use by the mother or spouse within 2 years, mother in drug rehabilitation program or infant exhibiting drug withdrawal. Alcohol and tobacco use was evaluated from maternal self-report through routine prenatal visit questionnaires. The timing and amount of exposure to alcohol and tobacco was not specifically evaluated. The study received exempt status from the hospital system's institutional review board.

Outcomes

The primary predictor was prenatal exposure to marijuana as defined by a positive meconium test for THC. Covariates collected included maternal age, race/ethnicity, self-reported alcohol/tobacco use, cervical insufficiency, multiple gestation, maternal diabetes and hypertension. Outcomes included gestational age, preterm birth, NICU admission, low birth weight (defined as less than 2.5 kg), birth weight, length, head circumference and Apgar scores. To examine the bivariate association between rates of preterm birth and NICU admission with prenatal marijuana exposure, we performed chi-square tests. To determine if there was an adjusted difference in birth weight, height and head circumferences between those with versus without prenatal marijuana exposure, we used two-sample t-tests. To control for type I error, we calculated p-values using the Benjamini and Hochberg false discovery rate correction. For outcomes with a significant ($p<0.05$) bivariate association with THC, we conducted multivariable regression analyses to control for important maternal and gestational factors, including tobacco use, alcohol use, diabetes, hypertension, cervical insufficiency, and multiple

Table 1. Patient characteristics, comorbidities, and risk factors by THC status, N=1540			
	Overall, N=1,540	**THC positive, n=483**	**No substance, n=1,057**
Patient characteristics			
Maternal age, mean(sd)	27.2(5.6)	26.5(5.1)	27.6(5.7)
Race and ethnicity, n(%)			
White	1231(79.9%)	408(84.5%)	823(77.9%)
Black	47(3.1%)	16(3.3%)	31(2.9%)
Hispanic	115(7.5%)	22(4.6%)	93(8.8%)
Other/Unknown	147(9.6%)	37(7.7%)	110(10.4%)
Comorbidities & Risk Factors			

gestation. For the dichotomous outcome of preterm birth, we utilized multivariable logistic regression. For the continuous outcomes of birth weight, length and head circumferences, we utilized multivariable linear regression.

Patient and public involvement:

Patients or the public were not involved in the design, conduct, or reporting of this study.

RESULTS

Population characteristics

There were 1,804 patients for which a meconium sample was screened, 101 (5.6%) of which were excluded for significant missing data (Figure 1). There were a total of 11,617 births in the hospital network during the study period, therefore close to 15% of all newborns had a meconium drug screen obtained. For the primary analysis we excluded patients whose sample contained any substances in addition to/other than THC (163, 9.6%) (supplement), leading to a final sample size of 1,540. THC was detected in 483 (31.3%) of meconium samples. Within this cohort, patients who tested positive for THC were more likely to be Caucasian, use tobacco and less likely to have diabetes (Table 1).

Tobacco use, n(%)	612(39.7%)	214(44.3%)	398(37.7%)
Alcohol use, n(%)	35(2.3%)	12(2.5%)	23(2.2%)
Diabetes, n(%)	211(13.7%)	53(11%)	158(15%)
Hypertension, n(%)	289(18.8%)	84(17.4%)	205(19.4%)
Cervical insufficiency, n(%)	19(1.2%)	4(0.8%)	15(1.4%)
Multiple gestation, n(%)	41(2.7%)	11(2.3%)	30(2.8%)

In unadjusted analyses, neonates who tested positive for THC had significantly lower birth weight, shorter length and smaller head circumference (p<0.003) (Table 2).

Table 2: Unadjusted outcomes by THC status, n=1,540

Outcomes	**Overall, N=1,540**	**THC positive, n=483**	**No substance, n=1,057**	**p-value***
Gestational age (weeks), mean(sd)	38.9(2.0)	38.9(1.7)	38.9(2.1)	0.651
Preterm birth (<37 weeks), n(%)	152(9.9%)	44(9.1%)	108(10.2%)	0.651
NICU admission, n(%)	189(12.3%)	56(11.6%)	133(12.6%)	0.651
Length (cm), mean(sd)	**50.1(3.1)**	**49.5(2.9)**	**50.3(3.2)**	**0.003**
Weight (kg), mean(sd)	**3.25(0.58)**	**3.13(0.56)**	**3.31(0.59)**	**0.003**
Low birth weight (<2.5kg), n(%)	**136(8.8%)**	**59(12.2%)**	**77(7.3%)**	**0.004**
Head Circumference (cm), mean(sd)	**34(2.2)**	**33.6(2.5)**	**34.2(2)**	**0.003**
5-minute Apgar, mean(sd)	8.7(0.7)	8.8(0.7)	8.7(0.7)	0.533

*t-tests for continuous data; chi-square tests for categorical data; reported p-values are corrected for multiple testing using the Benjamini and Hochberg false discovery rate correction

Marijuana exposed neonates were also more likely to be designated as low birth weight (<2.5kg).

Adjusted analysis

In the adjusted analysis, neonates exposed to THC had significantly lower birth weight, shorter length and smaller head circumference (p<0.001) (Table 3).

Table 3. Results from adjusted linear regression analyses, n=1,539

Model Covariates	**Birth weight** Regression	**P-value**	**Head circumference**	**p-value**	**Length** Regression	**p-value**

	Coefficient (95% CI)		Regression Coefficient (95% CI)		Coefficient (95% CI)	
THC positive	***-0.16(-0.22 to -0.10)***	***<0.001***	***-0.52(-0.78 to -0.27)***	***<0.001***	***-0.71(-1.03 to -0.39)***	***<0.001***
Patient characteristics						
Maternal age	***0.01(0.00 to 0.01)***	***0.032***	***0.02(0.01 to 0.04)***	***0.009***	0.02(-0.01 to 0.05)	0.159
Race/ethnicity						
White	referent	0.449	referent	0.861	referent	0.212
Black	-0.04(-0.21 to 0.12)		-0.01(-0.88 to 0.85)		-0.51(-1.65 to 0.62)	
Hispanic	-0.04(-0.15 to 0.07)		-0.09(-0.48 to 0.30)		-0.30(-0.99 to 0.40)	
Other/Unknown	0.06(-0.04 to 0.16)		-0.16(-0.56 to 0.25)		0.42(-0.09 to 0.93)	
Comorbidities & Risk Factors						
Tobacco use	***-0.15(-0.21 to -0.09)***	***<0.001***	***-0.41(-0.64 to -0.17)***	***0.001***	***-0.79(-1.12 to -0.46)***	***<0.001***
Alcohol use	-0.12(-0.31 to 0.07)	0.228	-0.78(-2.01 to 0.45)	0.214	-0.56(-1.48 to 0.36)	0.232
Diabetes	0.03(-0.05 to 0.11)	0.462	-0.01(-0.33 to 0.32)	0.957	0.14(-0.32 to 0.59)	0.550
Hypertension	***-0.18(-0.25 to -0.10)***	***<0.001***	***-0.36(-0.62 to -0.10)***	***0.008***	***-0.72(-1.14 to -0.29)***	***0.001***
Cervical insufficiency	-0.18(-0.43 to 0.08)	0.173	-0.48(-1.53 to 0.56)	0.362	-1.61(-3.52 to 0.30)	0.099
Multiple gestation	***-0.66(-0.84 to -0.49)***	***<0.001***	***-1.47(-2.13 to -0.81)***	***<0.001***	***-3.48(-4.49 to -2.47)***	***<0.001***

Multivariable linear regression controlled for tobacco use, alcohol use, diabetes, hypertension, cervical insufficiency, and multiple gestation.
Note: there was one patient missing age and was excluded from multiple regression models

Table 4. Results from adjusted logistic regression analyses, n=1,539

Model Covariates	Low birth weight OR (95% CI)	p-value

Birth weight was on average 0.16 kg lower (95% CI: 0.10 to 0.22, p<0.001) in those exposed to THC. Head circumference was on average 0.52 cm lower (95% CI: 0.27 to 0.78, p<0.001) in those exposed to THC. Length was on average 0.71 cm lower (95% CI: 0.39 to 1.03, p<0.001) in those exposed to THC. As compared to those unexposed to THC, those exposed had 1.9 times the odds (95% CI: 1.3-2.7, p=0.001) of being defined as low birth weight in the adjusted analysis (Table 4).

THC positive	***1.9(1.3-2.7)***	***0.001***
Patient characteristics		
Maternal age	1.0(1.0-1.0)	0.960
Comorbidities & Risk Factors		
Tobacco use	***1.8(1.2-2.6)***	***0.002***
Alcohol use	1.2(0.4-3.4)	0.792
Diabetes	1.6(1.0-2.6)	0.054
Hypertension	***1.6(1.0-2.4)***	***0.033***
Cervical insufficiency	2.9(0.9-9.2)	0.072
Multiple gestation	***5.7(2.8-11.4)***	***<0.001***

Multivariable logistic regression controlled for tobacco use, alcohol use, diabetes, hypertension, cervical insufficiency, and multiple gestation.
Note: there was one patient missing age and was excluded from multiple regression models.

There were no significant association between THC exposure and preterm birth, NICU admission, and Apgar scores. We were not able to include race in the multivariable analysis of dichotomous outcomes due to insufficient sample size. In preliminary adjusted logistic regression analyses, the p-value for race was >0.60 for all dichotomous outcomes and thus was chosen for removal.

We used robust standard errors for the analyses of head circumference and length due to evidence of heteroskedasticity of the residuals. All models were tested for multicollinearity which was not present. All other regression diagnostics indicated good model fit.

DISCUSSION

This study found that prenatal marijuana exposure was significantly associated with decreased birth weight, length and head circumference. In addition, infants exposed to marijuana were more likely to be defined as low birth weight compared to those unexposed.

Similar to many previous studies, our data showed a decreased birth weight in infants exposed to marijuana.[3,11,16-19] On average, the birth weight in infants exposed to marijuana in our cohort was 160 grams lower than in those unexposed and exposed infants were more likely to be classified as low birth weight. This finding is similar to previously published work demonstrating a higher incidence of low birth weight infants exposed to marijuana.[18,20,21] These findings are particularly relevant in terms of newborn care as it relates to the increased need for blood work and testing.[22] Increased newborn blood draws can be associated with breastfeeding disruption, hyperalgesia, and parental anxiety, underscoring the importance in ameliorating factors such as THC use that may contribute to lower birth weight.[23,24]

Our study further demonstrated a decreased birth length in infants exposed to marijuana. Previous studies evaluating this outcome have been contradictory.[3,6,19,25-27] In our cohort, infants exposed to marijuana were also more likely to have a decreased birth head circumference. Similarly, previous work evaluating this outcome has been conflicting.[3,6,19,25-28] The finding of decreased head circumference in the exposed group is potentially multifactorial. Previous studies have linked maternal alcohol use with decreased head circumference.[29] Given that alcohol use was self-reported, and potentially under reported, in our population, one could hypothesize that the decreased head circumference could be partially related to alcohol use.

Previous literature evaluating the effect of marijuana exposure on NICU admission is also inconsistent. Similar to previously reported data, our study did not show an increased risk of NICU admission in infants exposed to marijuana.[3,12,20] This is in contrast to research demonstrating an increased risk of NICU admission in infants exposed to marijuana.[16,18,21] Our study is also similar to previous literature which did not show an association with marijuana

exposure and preterm birth.[11,12,16,20,30] In contrast, other studies have shown an association with marijuana exposure and preterm birth.[31-33] Lastly, our study did not show a significant difference in the five minutes Apgar scores for THC exposed infants, which is consistent with previously reported studies.[3,17,26,27,34,35]

Our study used a potentially higher risk initial population due to the inclusion criteria for obtaining a meconium drug screen. However, both the study group (THC positive meconium) and comparison group (THC negative meconium) were derived from this initial population of infants that had a meconium collected. Meconium drug screens that were positive for drugs other than THC were excluded from the analysis. Therefore, the comparison group consisted of infants with completely negative meconium drug screens. The authors intentionally did not derive a comparison group from infants who did not have meconium collected given the concern that this may have introduced significant bias between the study and comparison group.

The etiology of discrepant findings of marijuana exposure on neonatal outcomes is likely multifaceted. Previous authors have hypothesized that the strong reliance on self-report of marijuana use could bias studies toward the null hypothesis by misclassifying marijuana users as non-users.[3] To our knowledge, our study is one of the largest in the United States ever to examine the effects of marijuana on neonates using targeted drug screen results, rather than maternal self-report.[11,12] As previously noted, in the metanalysis by Conner et al, 20 of the 31 studies included relied on maternal self-report of marijuana use.[3,12] Unlike the Gunn et al metanalysis, which included many studies that did not control for tobacco use, our study rigorously controlled for potential confounders such as tobacco use, increasing the ability to evaluate for the independent effect of marijuana on neonatal outcomes.[11] This ability to control for important confounders, large sample size, use of biochemical data to define THC use,

and the exclusion of polysubstance use may explain some of the differences found in our study compared to previous literature. Our findings underscore the importance in continued adherence to both AAP and ACOG guidelines which recommend counseling women against using marijuana during pregnancy. Our research adds to the growing literature demonstrating potential negative effects of marijuana use during pregnancy and highlights the need for continued national conversations regarding its widespread use.

This study has some limitations. The retrospective cohort design inherently limits the ability to determine causality. There was lack of racial diversity in the cohort and we were unable to include race in the multivariable analysis, possibly limiting generalizability. We were unable to assess the precise reason for a meconium screen being obtained other the general category of reasons previously enumerated, which may have introduced unmeasured confounders. Both alcohol and tobacco use were self-reported which may have resulted in the underreporting of exposure. We may have introduced selection bias by only examining neonates who had meconium drug screens rather than utilizing a cohort with universal testing. However, it could be hypothesized that if we had compared neonates without meconium drug screens, we may have found even greater differences. Future prospective studies could ameliorate this possible bias by studying cohorts that employ universal drug testing. As meconium screens primarily detect second and third trimester drug exposure, we did not evaluate early pregnancy drug use. There was no separation of maternal hypertensive disorders or maternal type of diabetes and there was no exclusion of anomalous fetuses or those with genetic disorders which may have introduced confounding. We did not exclude mothers taking medications associated with low birth weight or exclude mothers with autoimmune conditions which may have also introduced confounding.

Finally, we did not quantify marijuana exposure in our population which would have allowed for more granular interpretation and analysis.

CONCLUSIONS

To our knowledge, our study is one of the largest in the United States ever to examine the effects of marijuana on neonates using targeted drug testing results rather than maternal self-report. In our study, prenatal marijuana exposure was significantly associated with decreased birth weight, length, head circumference and risk of being low-birth weight after controlling for important confounders. These findings highlight the need for continued education of pregnant women and adherence to both AAP and ACOG guidelines in avoiding marijuana use in pregnancy.

Contributor Statements:

Dr. Jones conceptualized and designed the study, interpreted the data, drafted the initial manuscript, and approved the final manuscript as submitted.

Dr. Lotfi collected the initial data, interpreted the data, revised the manuscript, and approved the final manuscript as submitted.

Ms. Lin carried out the initial data analyses, interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Dr. Gievers, Dr. Hendrickson, and Dr. Sheridan reviewed and interpreted the data, revised the manuscript, and approved the final manuscript as submitted.

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Competing interests: None declared**.**

Patient consent for publication: Not applicable.

Ethics approval: The study received exempt status from the hospital system's institutional review board.

Data availability: Data are available upon reasonable request.

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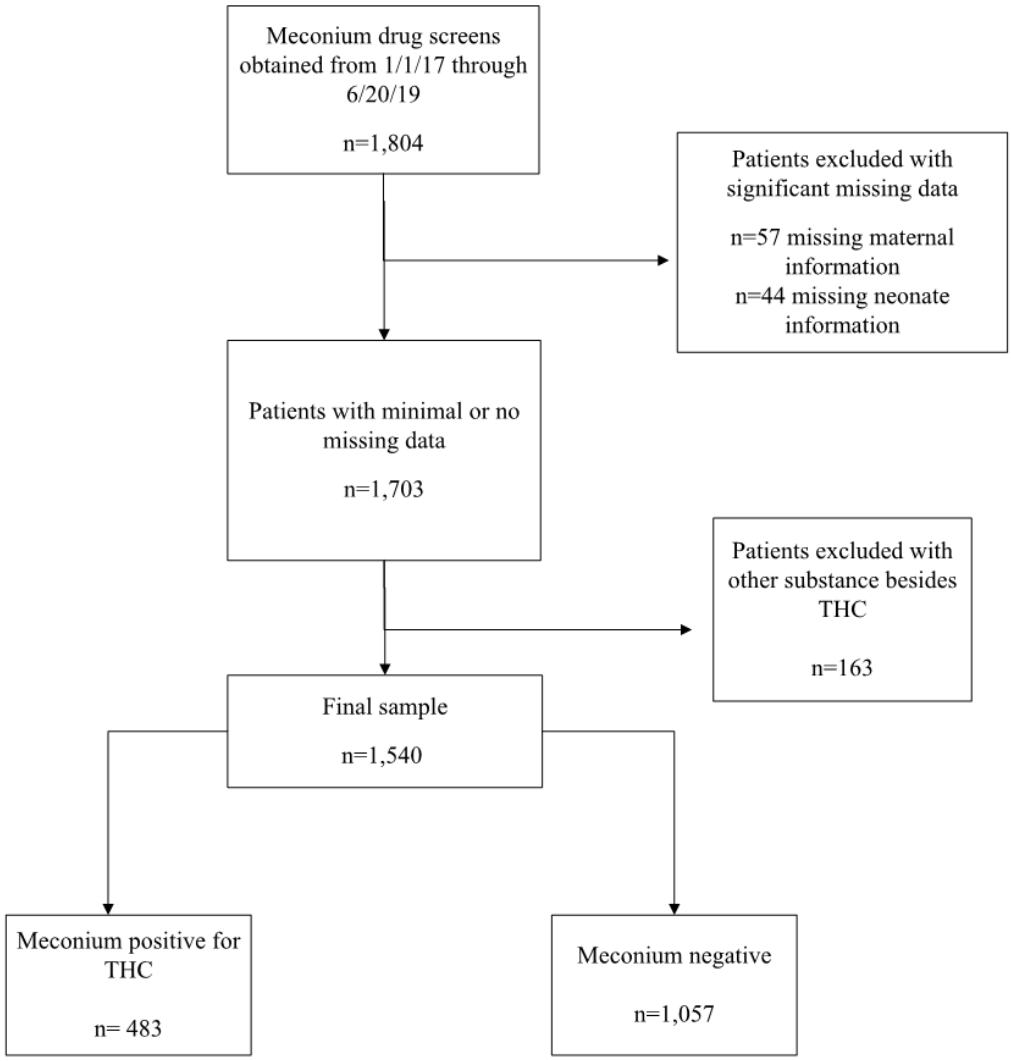
Figure Legend/Caption

Figure 1: Flowchart for Study Cohort. Inclusion criteria included all cases with meconium drug screens recorded. Cases were excluded if any other drug (other than delta-9-tetrahydrocannabinol (THC)) was detected in meconium and in charts with significant missing data.

Figure 1: Flowchart for study cohort



Presence of other drugs in meconium screen by THC status, n=1,703

	All patients, n=1,703	**THC negative, N=1,175**	**THC positive N=528**	**p-value**
Presence of one or more drugs (besides THC) in meconium screen, n(%)	163(9.6%)	118(10.0%)	45(8.5%)	0.324
Presence of drugs in meconium screen, n(%)				
Methamphetamines	84(4.9%)	60(5.1%)	24(4.6%)	0.621
Amphetamines	102(6.0%)	72(6.1%)	30(5.7%)	0.720
Barbiturates	1(0.1%)	1(0.1%)	0(0.0%)	0.503
Cocaine	4(0.2%)	2(0.2%)	2(0.4%)	0.411
Opiates	51(3.0%)	38(3.2%)	13(2.5%)	0.387
Oxycodone	6(0.4%)	4(0.3%)	2(0.4%)	0.902
Phencyclidine	0(0.0%)	0(0.0%)	0(0.0%)	NA
Methadone	29(1.7%)	24(2.0%)	5(1.0%)	0.106
Propoxyphene	0(0.0%)	0(0.0%)	0(0.0%)	NA
Benzodiazepines	0(0.0%)	0(0.0%)	0(0.0%)	NA

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	(a) 8 (b) 8 (c)8-9 (d)n/a (e)n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	(a)8-9 (b)8-9 (c)appendix
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	(a)8-9 (b)8-9
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-12

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(a)10-12 (b)11-12 (c)n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.