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Marijuana use, fetal growth, and uterine artery Dopplers

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Abstract

Objective: Marijuana (MJ) use is associated with adverse effects on fetal growth. We aimed to investigate the timing of suboptimal fetal growth onset in MJ-exposed pregnancies. In addition, we aimed to explore the relationship between MJ-exposure and both abnormal uterine artery (UtA) Doppler parameters and small for gestational age (SGA).

Study design: This was a secondary analysis of a prospective multicenter cohort that enrolled nulliparous individuals delivering non-anomalous fetuses beyond 20 weeks' gestation. Marijuana exposure was ascertained by self-report or clinical urine toxicology testing. Ultrasound estimated fetal weights (EFWs) were assessed in participants at both 16w0d–21w6d and 22w0d–29w6d. EFWs and birth weight (BW) were converted to weight percentiles (wPCT). EFW and BW wPCTs were calculated using population-based standards. Additionally, a customized standard designed to be applicable to both EFWs and BWs within the same model was also used to allow for EFW to BW percentile trajectories. The primary outcome, longitudinal wPCT, was compared between individuals with and without MJ use in a linear mixed-effects regression model adjusting for tobacco. For modeling, wPCT was smoothed across gestational age; MJ was estimated as an intercept and linear difference in the slope of gestational age. UtA Doppler notching, resistance index (RI), and pulsatility index (PI) at 16w0d–21w6d were compared using *t*-test and χ^2. SGA at delivery was also compared.

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Disclosure statement

The authors report no conflict of interest.

Results: Nine thousand one hundred and sixty-three individuals met inclusion criteria; 136 (1.5%) used MJ during pregnancy. Individuals who used MJ were more likely to be younger, identify as non-Hispanic Black, and have had less education. Fetuses exposed to MJ had lower wPCT beginning at 28 weeks using population-based and customized standards, when compared to those without exposure. UtA notching, PI, and RI were similar between groups. SGA was more frequent in neonates exposed to MJ using both population-based (22 vs. 9%, $p<.001$) and customized (25 vs. 14%, $p<.001$) curves.

Conclusions: MJ-exposed fetuses were estimated to be smaller than unexposed fetuses starting at 28 weeks' gestation across both growth standards without a difference in UtA Doppler parameters.

Keywords

Marijuana; fetal growth; birth weight; weight percentile; uterine artery Doppler

Introduction

Marijuana (MJ) is the most commonly used illicit drug in pregnancy, and tetrahydrocannabinol (THC), the main active compound in MJ, readily crosses the placenta [1-4]. Data on MJ use during pregnancy have demonstrated inconsistent effects on perinatal outcomes [5-7]. Despite recommendations against use during pregnancy and lactation from experts and the American College of Obstetricians and Gynecologists, legalization in many states across the U.S. has resulted in increased perinatal use [3,8]. Further understanding the effects of MJ exposure on fetal and neonatal outcomes is therefore critical for pregnancy counseling, management, and surveillance.

Evidence consistently supports an association between maternal MJ exposure during pregnancy and decreased fetal growth [6,7,9]. Studies on MJ and fetal growth have largely utilized the outcome of birthweight [6,10]. Marijuana exposure is associated with decreased fetal growth (as measured by antenatal ultrasound) in the late third trimester [11,12]. However, the gestational age at which MJ-associated alterations in fetal growth become detectable is not known. In the setting of limited evidence, guidelines do not currently recommend ultrasonographic fetal growth surveillance during pregnancy for MJ exposure alone [2,3].

Changes in uterine artery (UtA) Doppler parameters, which have been used as an early marker for placental resistance and in some studies associated with alterations in fetal growth, have not been explored for MJ use [13]. Understanding the relationship between UtA Doppler resistance and MJ exposure is valuable to both inform potential noninvasive screening measures in the MJ-exposed pregnancy and when considering the biologic pathway of the observed decrease in growth with MJ use.

The Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b) was a multicenter prospective observational cohort study that collected data regarding perinatal exposure to recreational substances, antenatal ultrasound measures, and clinical outcomes across pregnancy beginning in the first trimester [14]. We aimed to evaluate the timing

of onset of decreased fetal growth in MJ-exposed pregnancies as compared to unexposed pregnancies in the nuMoM2b cohort. We additionally aimed to evaluate whether MJ exposure was associated with abnormal UtA Doppler parameters and small for gestational age (SGA).

Materials and methods

This was a nuMoM2b secondary data analysis. The original study prospectively enrolled nulliparous individuals with singleton pregnancies from eight geographically diverse clinical centers across the U.S. between October 2010 and September 2013. Individuals were screened for eligibility and enrolled in the first trimester. Enrolled participants had three study visits: study visit one (6w0d to 13w6d), study visit two (16w0d to 21w6d), and study visit three (22w0d to 29w6d). Data collection included biometric measurements at each visit, fetal growth ultrasounds, blood and urine biospecimens, and medical record abstraction for maternal and neonatal outcomes. The study methodology was previously reported [14]. The parent study was approved by the institutional review board (IRB) for each clinical site. This secondary analysis included only de-identified data, and was considered exempt by the University of Utah IRB.

For the purposes of this analysis, all individuals with singleton deliveries >20 weeks' gestation were considered for inclusion. We excluded spontaneous miscarriages, terminations, and anomalous fetuses. We also excluded pregnancies missing key measurements for analysis including any UtA Doppler measurement, fetal/neonatal sex, birth weight (BW), and gestational age at delivery.

The primary exposure was MJ use during pregnancy. Participants were evaluated for self-reported past-month MJ use at study visits two and three, and at delivery. In individuals undergoing clinically indicated urine toxicology at delivery admission, biologically detected MJ use was confirmed by 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH) in urine. For this analysis, individuals with self-report at any time point or biologically detected MJ on clinical urine toxicology testing were categorized as MJ exposed.

The primary outcome was weight percentile (wPCT) which was measured longitudinally during pregnancy. Sonographic measurements of fetal biometry (i.e. biparietal diameter, head circumference, abdominal circumference, and femur diaphysis length) were used from the second and third study visit. Birth weight was collected at delivery. The ultrasound estimated fetal weight (EFW) from visits two and three, as well as neonatal BW, were converted to weight percentiles. The wPCTs were calculated using population-based standards of Hadlock for EFW from visit two and three ultrasounds, and Olsen for BW [15,16]. The Olsen standard utilizes gestational age, birthweight, and sex in the calculator and was chosen because it was adapted to calculate percentiles specific to the gestational day using methods previously described [16,17].

In a secondary analysis, we used a customized standard, Gestational Related Optimal Weight (GROW v8.0.6.1.2020, www.gestation.net), to calculate customized wPCTs. GROW was

used because it was designed to be applied to both EFWs and BWs and would, therefore, allow for assessment of EFW to BW percentile trajectories [18,19]. The GROW standard adjusts for maternal age, body mass index, race/ethnicity, and neonatal sex when calculating the weight percentile and was applied to EFWs at >20 weeks' gestation and BWs. The inclusion of race/ethnicity within clinical algorithms has been criticized for lack of biologic plausibility and representation of a socially constructed variable that perpetuates inequity [20,21]. Therefore, GROW BW percentages were calculated using a global average for race/ethnicity [22]. The GROW model does not compute calculations before 20 weeks' gestation, and therefore growth assessments occurring at less than 20 weeks were missing for secondary analysis.

Maternal demographic characteristics included in analysis were maternal age, body mass index (kg/m^2), comorbid conditions (chronic hypertension, diabetes), social determinants of health (self-identified race and ethnicity, education status, poverty category), and tobacco use. Tobacco exposure was defined as any self-reported use in the past month at the same study visits at which MJ use was assessed.

Secondary outcomes included UtA Doppler notching, pulsatility index (PI), and resistance index (RI). All participants underwent UtA Doppler assessment at visit two. Study procedures included sonographic sampling of one UtA by pulsed Doppler distal to the bifurcation. Waveform analysis required an image with at least three uniform waveforms present. The best image was selected for assessment with either autoor manual-tracing to measure RI and PI. A diastolic notch was defined as an upswing in the waveform at the beginning of diastole. A systolic notch was defined as a decrease in the rate of decline in maximal flow velocity during the decelerative phase of the systolic wave. The same procedures were completed on the opposite UtA. For this analysis, we considered the maximum RI and PI from either UtA, and any notching present on either UtA. The nuMoM2b study protocol required certification for all sonographers and physicians performing or interpreting ultrasounds in the study. This included either previous certification by the National Institute of Child Health and Human Development (NICHD) National Standard for Normal Fetal Growth Study (NFGS), or for those not previously certified, sonographers and physicians completed an equivalent nuMoM2b credentialing standard [14].

We also compared the frequency of SGA at delivery between MJ exposed and unexposed pregnancies. Analysis was completed using both the population-based growth curves and the customized GROW curve. SGA was defined as a modeled BW less than the 10th percentile for gestational age [23].

We compared characteristics of individuals who were exposed and those who were unexposed to MJ during pregnancy using chi square and *t*-test as appropriate. WPCT was compared between exposure groups at each study timepoint (visit two, visit three, and delivery) by two-sample *t*-test. For the primary analysis, wPCT was compared longitudinally between individuals with and without MJ use in a linear mixed-effects regression model. The mixed-effects regression modeling approach accounts for repeated observations across pregnancy for each delivery for the outcome measure wPCT. WPCT was smoothed across

gestational age with gestational age as a fifth order interaction, and MJ as an interaction in the linear term with gestational age. Tobacco exposure was considered a clinically significant covariate with adjustment for exposure included in the final model. Modeling was performed for both population-based wPCT, as well as for the customized wPCTs in secondary analysis [15,16,18,19]. The secondary outcomes of UtA Doppler notching, RI and PI, as well as SGA at delivery, were compared using *t*-test and chi square.

A *p* value <.05 was considered statistically significant. All analyses were completed using SAS 9.4 (Cary, NC) and graphics created using GraphPad Prism v8.3 (La Jolla, CA).

Results

The nuMoM2b prospective cohort study included 10,038 individuals. Following exclusion of 875 individuals for missing exposure or outcome data, 9163 remained for this analysis (Figure 1). Marijuana exposure was identified in 136 individuals (1.5%; 105 by self-report, 21 by clinical urine toxicology, and 10 by both methods). Self-reported MJ use was higher among individuals with an available urine toxicology test (12%) than those without an available clinical urine toxicology test (0.8%).

Marijuana use was more frequent among participants of younger age, who identified as non-Hispanic Black, and had lower educational attainment (Table 1). Tobacco use was more frequent among participants who used MJ compared with those who did not (52.2% vs. 6.1%, $p<.001$). There were no significant differences between MJ-exposed and unexposed individuals for comorbid conditions.

The mean wPCT at each gestational age analyzed using the population-based growth curve, was significantly lower among MJ exposed compared with unexposed at study visit three (43.2 ± 24.5% vs. 49.5 ± 26.2%, $p=.004$) and delivery (31.1 ± 23.0% vs. 43.3 ± 25.4%, p<.001, Table 2). Using the customized curve, the mean wPCT also became significantly lower in MJ-exposed compared to unexposed at study visit three (53.1 ± 28.1% vs. 59.2 ± 28.0%, $p=.014$), as well as at delivery (34.6 ± 29.2% vs. 45.0 ± 29.4%, $p<.001$).

In multivariable modeling, fetuses exposed to MJ had significantly lower wPCT for gestational age compared to unexposed fetuses beginning at 28 weeks' gestation using both the population-based and customized standard (Figure 2). Each model adjusts for tobacco use. The customized standard adjusts for maternal age, body mass index, and neonatal sex when calculating the weight percentile.

Uterine artery Doppler measurements were available and analyzed for 8243 individuals. UtA Doppler maximum RI and maximum PI did not differ between individuals with or without MJ exposure. Similarly, UtA Doppler notching did not differ between exposed versus unexposed (Table 2).

Using population-based curves, SGA was identified in 22% of MJ-exposed pregnancies as compared to 9% of unexposed pregnancies at delivery ($p<.001$). Similarly, SGA was more frequent in MJ-exposed as compared to unexposed pregnancies at delivery using the customized curve (25% vs. 14%, $p<.001$).

Discussion

We found MJ-exposed fetuses were smaller than unexposed using both population-based and customized standards for wPCT measured longitudinally across pregnancy and at delivery. The longitudinal growth in MJ-exposed fetuses became significantly lower at 28 weeks' gestation using both growth standards. UtA Doppler parameters were not different by MJ exposure. SGA was more prevalent in MJ-exposed compared with unexposed neonates.

Studies evaluating the relationship between MJ exposure and adverse fetal growth are subject to limitations including confounding from concomitant tobacco use and under-ascertainment of MJ use secondary to reliance on self-reported exposure alone. In studies that have adjusted for tobacco exposure and utilize both self-report and biologically confirmed MJ exposure, there is a consistent association between MJ and low BW [6,7,10,24,25]. Data are so robust that after systematically reviewing the literature, the National Academy of Sciences released a consensus document concluding there is ″substantial evidence″ supporting an association between maternal MJ use and low BW [9]. The timing of onset of fetal growth alterations in MJ-exposed pregnancies, however, remains unclear.

Two recent studies evaluated antenatal fetal growth in MJ-exposed pregnancies rather than BW outcomes alone. In a secondary analysis of a large population-based cohort study in the Netherlands, fetal ultrasound assessments were obtained in early-, mid-, and late-pregnancy with EFW percentile reported using Hadlock. Early pregnancy use of MJ was associated with lower estimated weights in late pregnancy (decrease by 57.7 g, 95% CI 28.7–86.7, $p<.001$) and lower BW (decrease by 156.6 g, 95% CI 89.2–224.0, $p<.001$) [11]. In a retrospective cohort study, Brar et al. compared fetal ultrasound growth parameters (Hadlock) in individuals exposed versus not exposed to MJ. Fetuses exposed to MJ, but not tobacco, as compared to controls demonstrated a statistically significantly lower EFW percentile in the third trimester (35.6 ± 21.9% vs. 52.5 ± 24.4%, $p<.001$) and increased frequency of third-trimester fetal growth restriction diagnosis [12]. Our findings of lower weight percentiles starting in the third trimester among fetuses of pregnancies in which MJ was used are consistent with these findings. We further evaluated temporality by utilizing longitudinal wPCT. Using this novel approach, we found that 28 weeks' gestation appears to be the gestational age when growth trajectories in MJ-exposed pregnancies begin to deviate from unexposed pregnancies.

We utilized both population-based and customized standards to evaluate wPCT over time. The Hadlock formula is the most widely used population-based fetal growth nomogram in the U.S. and has been demonstrated to predict BW percentile more accurately than more modern methods [26,27]. The Olsen curve was developed and validated in a large, racially diverse U.S. population and is similarly used as a standard growth nomogram for BW assessment [16,28]. Many advocate for customized rather than population-based standards to better account for individual characteristics, which may contribute to non-pathologic differences in growth and otherwise confound fetal size assessment [18,19]. In this study, the GROW customized standard was used in secondary analysis to allow better proximation of fetal to BW percentile trajectories, and explore the use of a customized growth curve

model for MJ-exposed pregnancies [18,19,29]. Our results were consistent across use of both growth curve methodologies.

UtA Dopplers are used to reflect placental resistance with elevated parameters, including PI greater than 95% for gestational age or notching, which are associated with preeclampsia and growth restriction [13,30-32]. Endothelial dysfunction and spiral artery remodeling are part of the pathophysiologic pathway leading to these conditions, which explains the attention to UtA Doppler changes as potential early markers for such conditions [30,31]. Early antenatal MJ exposure could plausibly affect placental physiology as MJ readily crosses the placenta [33]. However, we found that MJ-exposed pregnancies were not more likely to have UtA Doppler evidence of resistance to flow compared to MJ unexposed pregnancies. Taken together with the finding that growth did not become significantly different until the third trimester, the lack of notable UtA Doppler differences suggest that MJ-associated fetal growth changes may occur via a different pathway than early-onset placental insufficiency.

The association between MJ exposure and SGA has previously been established [6,9,10,24]. Our aim was to focus on the temporality of onset of adverse growth in this study. However, we did secondarily assess SGA at delivery, and our findings are consistent with previous literature. Neonates exposed to MJ were more likely to be SGA using both the population and customized curves.

NuMoM2b data were collected prospectively by trained perinatal research staff following a pre-specified protocol [14]. Strengths of our study included the universal use of serial, prospectively performed antenatal ultrasounds for fetal weight and BW to evaluate the temporality of decreased fetal growth. We assessed MJ use from self-report or clinically available urine toxicology screening at delivery to improve ascertainment of MJ exposure. We planned *a priori* to adjust for concomitant tobacco use in the regression model as tobacco has known deleterious effects on fetal growth [34,35]. In the setting of controversy regarding the best approach to assessment of growth using different standards, we utilized both population-based and customized standards to evaluate our primary outcome. Population-based BW percentiles were calculated to the gestational day, which conferred an additional degree of precision that is not available to studies assessing BW percentile using whole gestational weeks. The nuMoM2b study was a multicenter cohort covering a wide swath of the geographic U.S. which makes it a more representative sample and supports the generalizability of these findings. Finally, we explored UtA Doppler velocimetry to gain insights into the placental processes underlying MJ-associated fetal growth changes.

Our study has limitations. Biologic specimen confirmation for MJ exposure at delivery was utilized in addition to self-report, but specimen confirmation was only available in a small subset of the study population, making under-ascertainment of the exposure likely. Marijuana prevalence in pregnancy by self-report is 2–5% [1]. We identified a self-reported prevalence on the low end of this range. Others show that biospecimen confirmed estimates of MJ use are higher as compared to self-report [36]. Self-reported MJ use was not obtained at visit one, limiting our understanding of early pregnancy exposure. Marijuana use typically decreases across gestation [37,38]; therefore, those with ongoing use at the time of visit two

may be those with heavier use, and results may therefore demonstrate a larger discrepancy than would be seen with lower frequency of MJ use, or cessation early in pregnancy. We do not have data on the amount, route, or frequency of MJ use in the study population. We therefore could not consider a dose–response relationship between MJ and fetal growth. Urine toxicology data were only available at delivery further limiting the understanding of length of MJ-exposure. We evaluated and adjusted for tobacco co-use, but we were unable to quantify the amount of tobacco use. We did not assess the contribution of polysubstance use beyond tobacco, although this is historically low in pregnancy cohorts. Despite utilizing a large prospective cohort, our sample size for the exposed group is relatively small, due to the low prevalence of MJ exposure identified in our cohort.

Antenatal exposure to MJ is associated with decreased fetal growth, although the pathway between exposure and growth outcomes is not fully understood. Our study adds to our understanding of the temporality of this relationship by noting that prenatal MJ exposure is associated with smaller fetal measurements starting at 28 weeks' gestation. While this study demonstrates an association between MJ use and slower fetal growth, causation cannot be determined and our findings should not change clinical practice or recommendations for antenatal surveillance. Further study on the relationship between MJ exposure and fetal growth would be strengthened by the use of universal biologic sampling to confirm MJ exposure, and further exploration of the dose–response relationship between MJ exposure and fetal growth.

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Data availability statement

The Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b) dataset is housed in the Data and Specimen Hub (DASH) of the National Institutes of Health (NIH). It can be found at: https://dash.nichd.nih.gov/study/226675.

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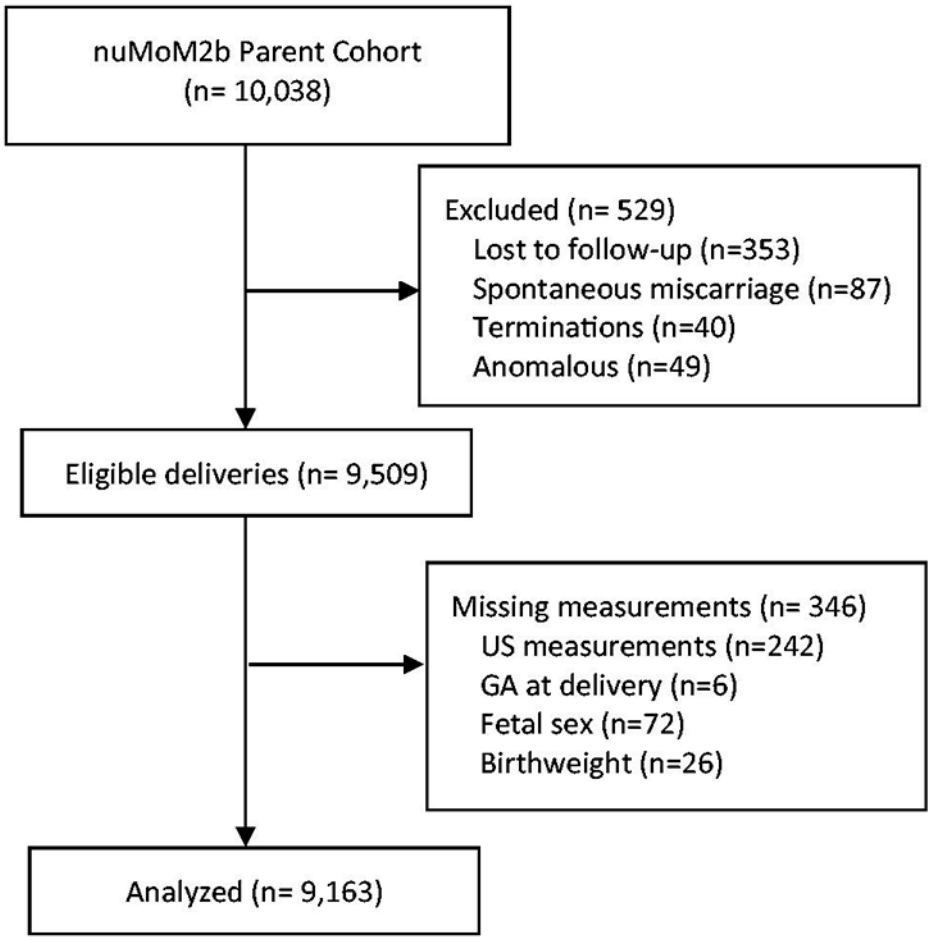

Figure 1.
Study population.

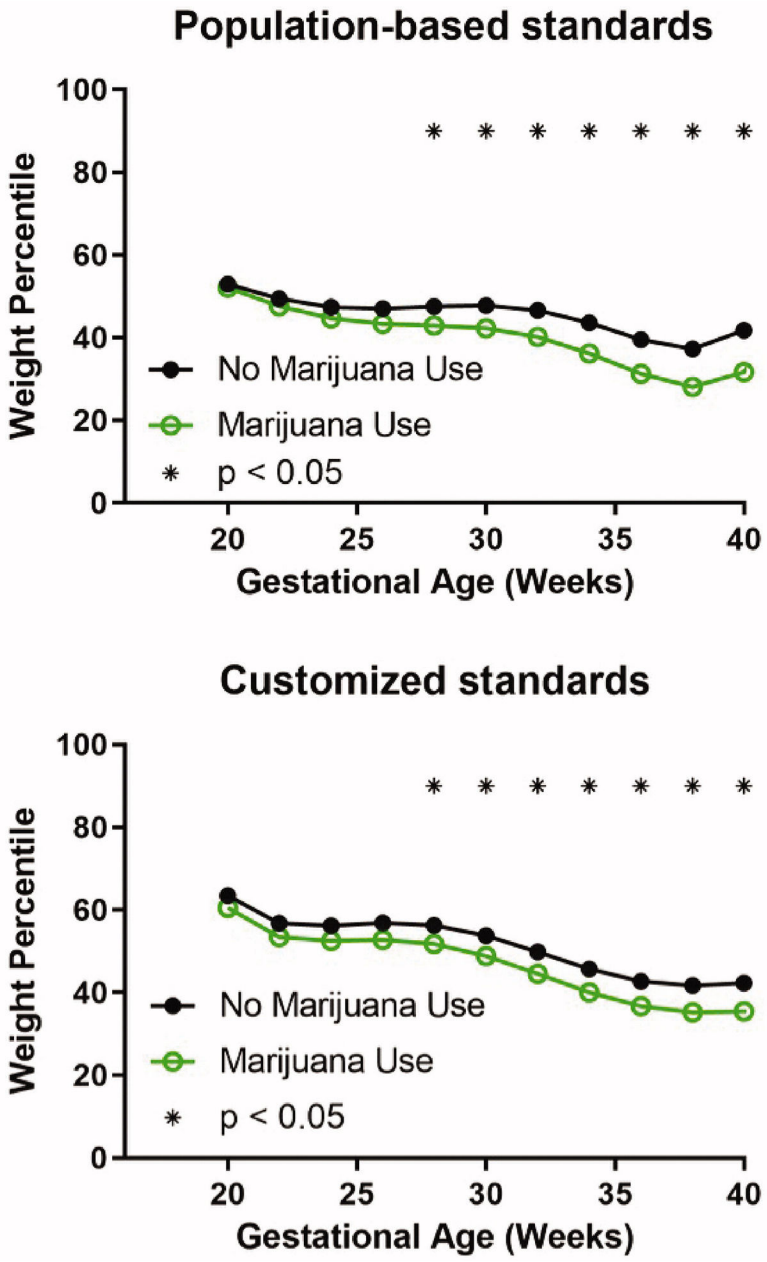

Figure 2.

Adjusted results for longitudinal weight percentiles (wPCT) for marijuana exposed compared with marijuana unexposed fetuses across gestation using population-based growth standards and customized standards.

Table 1.

Characteristics of the study population by marijuana exposure.

Characteristic	Marijuana exposure *N* = 136	No marijuana exposure *N* = 9027	*p*
Age (years)	22.9 (22.14, 23.62)	26.5 (26.36, 26.60)	<.001
Race/ethnicity			
Non-Hispanic White	54 (39.7)	5543 (61.4)	<.001
Non-Hispanic Black	54 (39.7)	1181 (13.1)	
Hispanic	13 (9.6)	1480 (16.4)	
Asian	0 (0.0)	372 (4.1)	
Other	15 (11.0)	448 (5.0)	
Education status			
<High school graduate	31 (22.8)	686 (7.6)	<.001
High school graduate	40 (29.4)	1009 (11.2)	
Some college	40 (29.4)	1699 (18.8)	
Technical degree	15 (11.0)	917 (10.2)	
College graduate	9 (6.6)	2558 (28.4)	
Degree beyond college	1 (0.7)	2153 (23.9)	
Poverty category			
>200%	18 (22.0)	5267 (71.2)	<.001
100–200%	19 (23.2)	1038 (14.0)	
<100%	45 (54.9)	1091 (14.8)	
Tobacco use	71 (52.2)	550 (6.1)	<.001
BMI[a] (kg/m^2)	25.7 (24.6, 26.9)	25.7 (25.6, 25.8)	.897
Chronic hypertension	5 (3.7)	227 (2.5)	.394
Pre-gestational diabetes	3 (2.2)	139 (1.5)	.534

Data presented as mean (95% confidence interval) or *n* (%).

[a]Body mass index.

Table 2.

Uterine artery Doppler indices and unadjusted weight percentile (wPCT) for gestational age using population-based and customized growth standards in the study population by marijuana exposure.

	Marijuana exposure	No marijuana exposure	*p* Value
Uterine artery Doppler measurement[*]			
	N = 121	*N* = 8122	
Maximum resistance index (RI)[a]	0.63 (0.61, 0.65)	0.61 (0.61, 0.62)	.149
Maximum pulsatility index (PI)[a]	1.19 (1.11, 1.27)	1.14 (1.13, 1.15)	.253
Any notch present[b]	23 (19.0)	1495 (18.4)	.865
Growth curve visit	Unadjusted weight percentiles (wPCT)		
	N = 136	*N* = 9027	
Population standard			
Study visit 2[c]	53.3 (25.1)	55.9 (25.2)	.233
Study visit 3[c]	43.2 (24.5)	49.5 (26.2)	.004
Delivery[c]	31.1 (23.0)	43.3 (25.4)	<.001
Customized standard			
Study visit 2[c]	55.9 (29.6)	63.7 (27.4)	.105
Study visit 3[c]	53.1 (28.1)	59.2 (28.0)	.014
Delivery[c]	34.6 (29.2)	45.0 (29.4)	<.001

[*] Uterine artery Doppler measurements available on fewer than the full cohort.

Data presented as

[a] mean (95% confidence interval)

[b] *n* (%), and

[c] mean (standard deviation).