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Clinical Research Article

Fetal Exposure to Cannabis and Childhood Metabolic Outcomes: The Healthy Start Study

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Abstract

Objective: To assess the impact of fetal exposure to cannabis on adiposity and glucose-insulin traits in early life.

Research Design and Methods: We leveraged a subsample of 103 mother-child pairs from Healthy Start, an ethnically diverse Colorado-based cohort. Twelve cannabinoids/metabolites of cannabis (including Δ9-tetrahydrocannabinol and cannabidiol) were measured in maternal urine collected at ~27 weeks' gestation. Fetal exposure to cannabis was dichotomized as exposed (any cannabinoid > limit of detection [LOD]) and not exposed (all cannabinoids < LOD). Fat mass and fat-free mass were measured via air displacement plethysmography at follow-up (mean age: 4.7 years). Glucose and insulin were obtained after an overnight fast. Generalized linear models estimated the associations between fetal exposure to cannabis with adiposity measures (fat mass [kg], fat-free mass [kg], adiposity [fat mass percentage], body mass index [BMI], and BMI *z*-scores) and metabolic measures (glucose [mg/dL], insulin [uIU/mL], and homeostatic model assessment of insulin resistance [HOMA-IR]).

Results: Approximately 15% of the women had detectable levels of any cannabinoid, indicating fetal exposure to cannabis. Exposed offspring had higher fat mass (1.0 kg; 95% CI, 0.3-1.7), fat-free mass (1.2 kg; 95% CI, 0.4-2.0), adiposity (2.6%; 95% CI, 0.1-5.2), and fasting glucose (5.6 mg/dL; 95% CI, 0.8-10.3) compared with nonexposed offspring. No associations were found with fasting insulin (in the fully adjusted model), HOMA-IR, BMI, or BMI *z*-scores.

Conclusions: We provide novel evidence to suggest an association between fetal exposure to cannabis with increased adiposity and fasting glucose in childhood, a finding that should be validated in other cohorts.

Key Words: DOHaD, fetal origins, pregnancy, cannabis, THC, CBD, child, obesity, glucose, insulin, metabolic syndrome

Abbreviations: BMI, body mass index; CB_1, cannabinoid type 1 receptor; CB_2, cannabinoid type 2 receptor; CBC, cannabichromene; CBD, cannabidiol; CBDV, cannabidivarin; CBG, cannabigerol; CBN, cannabinol; HOMA-IR, homeostatic model assessment of insulin resistance; LOD, level of detection; THC, Δ9-tetrahydrocannabinol; THC-C-gluc, Δ9-tetrahydrocannabinol glucuronide; THC-COOH, carboxylated form of Δ9-tetrahydrocannabinol; THCV, Δ9-tetrahydrocannabivarin

Cannabis use among pregnant women in the United States is on the rise. Between 2002 and 2017, self-reported use more than doubled (from 3.4% to 7.0%) (1). However, self-report may underrepresent actual use. A 2016 study in Colorado revealed that 22.4% of the pregnant women had detectable levels of the carboxylated form of Δ9-tetrahydrocannabinol (THC-COOH) in umbilical cord tissue, whereas only 2.6% self-reported use (2).

The increasing use of cannabis among pregnant women is not without risks. Neonates born to active cannabis users may be more likely to experience intrauterine growth restriction and low birth weight (3, 4). Growth-restricted offspring can experience excessive postnatal catch-up growth, a pattern that is associated with an increased risk for obesity (5), metabolic syndrome (6), and type 2 diabetes (7) later in life.

However, the potential impact of fetal exposure to cannabis on metabolic outcomes in the offspring is poorly understood. A recent study by Gillies and colleagues (8) demonstrated that fetal exposure to THC was associated with reduced β-cell mass and glucose intolerance among female Wistar rat offspring. In a large population-based cohort study, Cajachagua-Torres and colleagues (9) observed that self-reported maternal or paternal cannabis use during pregnancy was associated with higher body mass index (BMI) among the 10-year-old offspring. However, they reported no association with nonfasting glucose levels. Given the paucity of data, there is a need to further examine this novel research question, particularly in early childhood.

We used a subsample of mother-child pairs from Healthy Start, an ethnically diverse prebirth cohort based in Colorado, to explore this novel research question. Fetal exposure to cannabis was determined by the detection of 12 cannabinoids and cannabinoid metabolites in stored maternal urine samples collected mid-gestation. We hypothesized that fetal

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exposure to cannabis would be associated with increased adiposity and markers of impaired glucose homeostasis in early childhood.

Research Design and Methods

Healthy Start is an ethnically and racially diverse cohort of 1410 mothers and their offspring born between 2010 and 2014. Pregnant women were recruited from the outpatient obstetrics clinics at the University of Colorado Hospital before 24 weeks of gestation. Women were excluded from this study if they were expecting multiple births or had preexisting diabetes, asthma, cancer, or psychiatric illness. Enrolled pregnant women were invited to participate in 3 pregnancy visits at ~17 weeks' gestation, ~27 weeks' gestation, and delivery. A follow-up visit occurred in person when children were a mean of age ~4.7 years (SD: 0.5 years). Written informed consent was obtained from the mother or legal guardian of the child before each research visit. The protocol was approved by the Colorado Multiple Institution Review Board and the University of Texas Health Science Center Committee for the Protection of Human Subjects.

Fetal Exposure to Cannabis

Twelve cannabinoids and metabolites were measured in stored urine samples collected from a convenience sample of 199 mothers at ~27 weeks' gestation. Samples were analyzed on an Agilent 1200 HPLC system and AB SCIEX API5000 tandem mass spectrometer, as previously described (10). Detection was performed in positive atmospheric pressure chemical ionization mode. The analytes measured were as follows: THC, 11-hydroxy-THC, THC-COOH, THC-9-carboxylic acid glucuronide (THC-C-gluc), THC glucuronide (THC-gluc), cannabidiol (CBD), CBD glucuronide, cannabichromene (CBC), cannabinol (CBN), cannabigerol (CBG), Δ9-tetrahydrocannabivarin (THCV), and cannabidivarin (CBDV).

The proportion of participants with detectable levels of the individual cannabinoids ranged from 0% to 12% (THC-C-gluc). Fetal exposure to cannabis was dichotomized as exposed (where any cannabinoid or its metabolite exceeded the limit of detection [LOD]) and not exposed (where no cannabinoid or cannabinoid metabolites were detected or were below the LOD).

Metabolic Measures

At the childhood follow-up visit, trained phlebotomists obtained blood draws (~10 mL) after an overnight fast. Glucose was analyzed using a Beckman Coulter Instrument. Insulin was assayed using an automated radioimmunoassay (Millipore). The homeostatic model assessment of insulin resistance (HOMA-IR) was used to estimated insulin sensitivity from fasting glucose and insulin concentrations (11). HOMA-IR was calculated as (fasting insulin [uU/mL] × fasting glucose [mg/dL]) divided by 405.

Adiposity Measures

Childhood fat mass and fat-free mass were measured via whole body air displacement plethysmography (BodPod, Life Measurement, Inc.). The BodPod body composition systems use densitometric techniques to measure total body mass and 2 compartments in the offspring: fat mass (adipose tissue) and fat-free mass. Childhood adiposity (fat mass percentage) was calculated as a proportion of the fat mass divided by total mass. Fat mass and fat-free mass were conducted twice. A third examination was conducted if fat mass percentage differed by > 2%. The mean of the 2 closest measures was taken. Childhood height was measured to the nearest 0.1 cm using a stadiometer with a fixed vertical backboard and an adjustable headpiece. Childhood weight was measured to the nearest 0.1 kg using an electronic scale. Childhood BMI was calculated by dividing weight in kilograms by height in meters squared. BMI-for-age *z*-scores were calculated based on the US Centers for Disease Control and Prevention growth charts for children > 2 years.

Covariates

Maternal age at delivery was calculated based on offspring delivery date and maternal date of birth. Maternal education, race, ethnicity, and annual household income were collected via questionnaires. Prepregnancy BMI was calculated from maternal weight and height measured at the first prenatal visit. Gestational weight gain was measured across the 3 pregnancy research visits, during which maternal weight was measured.

Cotinine (the major metabolite of nicotine) was measured in maternal urine collected at ~27 weeks' gestation and in childhood at age ~4.7 years. Cotinine was measured via solid-phase competitive ELISA, with a sensitivity of 1 ng/mL (Calbiotech Cotinine ELISA CO096D). The limit of detection was 0.05 ng/mL. Fetal exposure to tobacco was dichotomized as no exposure (cotinine < LOD) and any exposure (cotinine ≥ LOD, indicating maternal active smoking or exposure to secondhand smoke). Childhood exposure to tobacco was dichotomized as no exposure (cotinine < LOD) and any exposure (cotinine ≥ LOD).

At infant age of ~5 months, women were asked in separate questions if they had ever breastfed their infant, were currently feeding their infant any breast milk, had ever fed their infant formula, or were currently feeding their infant formula. A measure of breast milk-months was developed that incorporated duration and exclusivity, as previously described (12). Briefly, this metric reflects duration of exclusive breastfeeding, where 6 months of exclusive breastfeeding equates to 6 breast milk-months, whereas 4 months of exclusive breastfeeding followed by 2 months of mixed feeding equates to 5 breast milk-months.

Childhood diet was measured via 24-hour dietary recalls (1 weekend and 2 weekdays), with mothers as proxy. Total caloric intake (kcal per day) was determined by the Nutrition and Obesity Research Center at University of North Carolina at Chapel Hill using the Nutrition Data System for Research software package. Child physical activity (steps per day) was measured by wGT3X-BT ActiGraph accelerometers (Pensacola, FL) worn for 7 days during waking hours on the waist.

Statistical Analysis

Generalized linear models estimated the associations between fetal exposure to cannabis (not exposed, exposed) and adiposity measures (fat mass [g], fat-free mass [g], adiposity [fat mass percentage], BMI, and BMI *z*-scores) and metabolic measures (fasting glucose [mg/dL], insulin [uIU/mL], and HOMA-IR) at age ~4.7 years. Fat mass, fat-free mass, fasting

glucose, insulin, and HOMA-IR were right-skewed and a log link function was used for these outcomes. Covariates were determined a priori based on previously reported associations with childhood metabolic outcomes and/or cannabis use during pregnancy. Our base models adjusted for maternal race and ethnicity (Hispanic, non-Hispanic black, non-Hispanic other, and non-Hispanic White), household income (< $40,000, $40,001-$70,000, ≥ $70,000, missing/declined to answer), offspring sex, fetal exposure to tobacco (cotinine < LOD, cotinine ≥ LOD), maternal prepregnancy BMI (kg/m^2), gestational weight gain (kg), gestational age at birth (weeks), birthweight (g), child age at the childhood follow-up visit (years), and childhood BMI (for the outcomes of fasting glucose, insulin, and HOMA-IR). Our final models additionally included the duration of exclusive breastfeeding (breast milk-months) and childhood exposure to tobacco (cotinine < LOD, ≥ LOD). We present adjusted means and beta coefficients with corresponding 95% CIs. Stata version 14.2 (StataCorp LP, College Station, TX, USA) was used for all analyses. The criterion for significance was set at $P < 0.05$.

Sensitivity Analyses

Fetal exposure to tobacco has been independently linked to insulin resistance in the offspring (13). Given that many participants in our cohort had both exposures, this raises the concern that tobacco, rather than cannabis, is driving these associations. As a secondary analysis, we present the results for the association between fetal exposure to tobacco and childhood metabolic outcomes while adjusting for fetal exposure to cannabis.

Furthermore, childhood diet and physical activity may also influence these associations. These covariates were not included in our fully adjusted models because many of mother-child pairs were missing information about childhood diet and physical activity. To compare results of models with and without these covariates, we also limited our main effects analyses to those with information about childhood diet and physical activity in sensitivity analyses (n = 63 for body composition outcomes; n = 56 for metabolic outcomes).

Results

The current cannabinoid analysis was conducted as a pilot study among a subsample of participants. Of the 1410 participants initially enrolled in the Healthy Start cohort study, the cannabinoid analysis was conducted in a convenience sample of 199 participants with stored maternal urine samples collected at ~27 weeks' gestation. For the adiposity analysis, 85 participants (of the 199 eligible participants) did not undergo the BodPod assessment and an additional 11 participants were missing information about gestational age at birth (n = 10) or gestational weight gain (n = 1). Thus, the analytic sample for the adiposity analysis was 103 participants. For the metabolic outcomes analysis, 102 participants (of the 199 eligible participants) did not have a fasting blood draw the follow-up visit and additional participants were missing information on gestational weight gain (n = 8) and childhood BMI (n = 1). Thus, 88 participants were included in the analytic sample for the metabolic outcomes. As compared with the overall cohort (n = 1410), mothers in the analytical samples were slightly older, more likely to have a household income ≥$70 000, and less likely to have detectable levels of urinary cotinine at mid-gestation (results not presented). The analytic samples had a slightly higher proportion of female offspring. There were no meaningful differences with respect to maternal age, prepregnancy BMI, gestational weight gain, maternal education, birthweight, or gestational age at birth. Compared with the analytical samples (n = 103 for body composition outcomes; n = 88 for metabolic outcomes), mother-child pairs included in the sensitivity analyses adjusting for childhood diet and physical activity (n = 63 for body composition outcomes; n = 56 for metabolic outcomes) were more likely to be non-Hispanic White and have a household income ≥$70,000 (results not presented).

Participants in our analytic sample were racially and ethnically diverse, with mothers identifying as 59% non-Hispanic White, 27% Hispanic, 7% non-Hispanic Black, and 7% from all other racial and ethnic groups combined (Table 1). A majority of mothers had some college education (77%) and a household income ≥$70 000 (49%).

Approximately 15% of the mothers had detectable levels of any cannabinoid at ~27 weeks' gestation, indicating fetal exposure to cannabis. There were some univariate differences in participants by exposure status. Compared with those with no exposure, offspring were more likely to be female ($P = 0.02$) and born at a lower birth weight ($P < 0.01$). Exposed offspring were more likely to have been concurrently exposed to tobacco in utero ($P < 0.01$), as well as during early childhood ($P = 0.03$). There were no meaningful differences in maternal age, prepregnancy BMI, gestational weight gain, maternal race/ethnicity, household income, maternal education, gestational age at birth, the duration of exclusive breastfeeding, and the child's age at the follow-up visit between the exposure groups.

The 12 cannabinoids and metabolites are summarized in Table 2. THC and its metabolites (11-hydroxy-THC, THC-COOH, THC-C-gluc, and THC-gluc) were generally more readily detectable than the other cannabinoids (THCV, CBD, CBC, CBN, CBG, and CBDV). The most common detectable cannabinoid was THC-C-gluc (n = 12). The highest concentration of any cannabinoid was THC-C-gluc, with a maximum concentration of 778.9 ng/mL.

Fetal exposure to cannabis was associated with increased fat mass, fat-free mass, and adiposity in early childhood (Table 3). Offspring with fetal exposure to cannabis had a 0.7-kg higher fat mass at age ~4.7 years compared with offspring without this exposure (95% CI, 0.2-1.2; $P = 0.01$; adjusted for maternal age, household income, maternal race/ethnicity, maternal education, offspring sex, fetal exposure to tobacco, prepregnancy BMI, gestational weight gain, gestational age at birth, birthweight, and child age at follow-up visit). This finding was robust after additional adjustment for the duration of exclusive breastfeeding and childhood exposure to tobacco (adjusted beta coefficient: 1.0; 95% CI, 0.3-1.7; $P < 0.01$). A similar pattern was observed for the outcome of fat-free mass. Fetal exposure to cannabis was associated with a 2.6% greater fat mass percent in childhood in the fully adjusted model (95% CI, 0.1-5.2; $P = 0.04$). No statistically significant associations were found between fetal exposure to cannabis and childhood BMI and BMI *z*-scores.

We found consistent associations between fetal exposure to cannabis and higher glucose levels in childhood (Table 4). Compared with nonexposed offspring, exposed offspring had fasting glucose levels that were on average 8.0 mg/dL higher

Table 1. Characteristics of eligible mothers and children in the Healthy Start study

	Fetal exposure to cannabis[a]			
	All (n = 103)	**Not exposed (n = 88)**	**Exposed (n = 15)**	***P* value**
Mother characteristics				
Age (y)	30 ± 6	30 ± 5	27 ± 7	0.05
Prepregnancy BMI (kg/m^2)	25 ± 5	25.4 ± 5.3	24.8 ± 4.7	0.66
Gestational weight gain (kg)	13.1 ± 5.5	12.9 ± 5.5	15.4 ± 5.8	0.33
Race/ethnicity				
Hispanic	28 (27%)	24 (27%)	4 (27%)	
Non-Hispanic Black	7 (7%)	4 (5%)	3 (20%)	
Non-Hispanic other	7 (7%)	6 (7%)	1 (7%)	
Non-Hispanic White	61 (59%)	54 (61%)	7 (47%)	0.17
Household income				
< $40,000	26 (25%)	19 (22%)	5 (33%)	
$40,001-$70,000	15 (15%)	13 (15%)	2 (13%)	
≥ $70,000	50 (49%)	45 (51%)	7 (47%)	
Missing/declined to answer	12 (12%)	11 (13%)	1 (7%)	0.22
Highest level of education				
<High school	12 (12%)	8 (9%)	4 (27%)	
High school degree	12 (12%)	11 (13%)	1 (7%)	
Some college or more	79 (77%)	69 (78%)	10 (67%)	0.13
Fetal exposure to tobacco (maternal cotinine at ~27 weeks' gestation)				
<LOD	88 (85%)	80 (91%)	8 (54%)	
≥LOD	15 (15%)	8 (9%)	7 (47%)	< 0.01
Infant characteristics				
Sex				
Male	49 (48%)	46 (53%)	3 (20%)	
Female	54 (52%)	42 (48%)	12 (80%)	*P* = 0.02
Birth weight (g)	3,259 ± 535	3,328 ± 507	2,853 ± 529	*P* < 0.01
Gestational age at birth (wl)	39.1 ± 2.1	39.1 ± 2.1	38.9 ± 1.7	*P* = 0.78
Duration of exclusive breastfeeding (breast milk-months; n = 95)				
Child characteristics				
Age at follow-up visit (y)	4.7 ± 0.5	4.7 ± 0.5	4.8 ± 0.2	*P* = 0.37
Childhood exposure to secondhand smoke (child cotinine at ~4.6 years; n = 96)				
<LOD	74 (77%)	67 (81%)	7 (54%)	
≥LOD	22 (23%)	16 (19%)	6 (46%)	*P* = 0.03

Continuous variables are expressed as means ± SD. Independent samples *t* tests were used to examine the differences in means by cotinine categories. Categorical variables are expressed as proportions of column totals. χ^2 tests were used to examine differences in proportions by cotinine categories.
Abbreviations: BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; LOD, limit of detection.
[a]Fetal exposure to cannabis was determined by the detection of twelve cannabinoids/metabolites of cannabis in maternal urine collected at ~27 weeks' gestation. The categories of were as follows: exposed (any of the measured cannabinoids exceeded the LOD) and not exposed (all of cannabinoids measured were below the LOD).

at age ~4.7 years (95% CI, 0.1-15.8; *P* = 0.04; adjusted for maternal age, household income, maternal race/ethnicity, maternal education, offspring sex, fetal exposure to tobacco, prepregnancy BMI, gestational weight gain, gestational age at birth, birthweight, child age at follow-up visit, and childhood BMI *z*-scores). After additional adjustment for the duration of exclusive breastfeeding and childhood exposure to tobacco, the mean difference in fasting glucose levels across exposure categories was slightly lower but remained statistically significant (adjusted beta coefficient 5.6; 95% CI, 0.8-10.3; *P* = 0.02). Fetal exposure to cannabis was also associated with higher fasting insulin in the base model (adjusted beta coefficient 4.0; 95% CI, 0.7-7.3; *P* = 0.02). However, the results were attenuated to nonsignificant after adjusting for postnatal factors (adjusted beta coefficient 2.2; 95% CI, -0.4 to 4.8; *P* = 0.10). Post hoc analyses revealed that this attenuation was due to the exclusion of participants who did not have information about the duration of exclusive breastfeeding (n = 8; results not presented). We did not find a statistically significant association between fetal exposure to cannabis and HOMA-IR.

Sensitivity Analyses

Fetal exposure to tobacco was associated with a 1.1 unit increase in childhood BMI *z*-scores (95% CI, 0.2-2.0; *P* = 0.01) but 12.9 mg/dL lower fasting glucose (95% CI, -23.6 to -2.2; *P* = 0.02) (results not presented). Fetal exposure to tobacco did not influence fat mass, fat-free mass, adiposity, BMI, fasting insulin, or HOMA-IR (results not presented).

Table 2. Urinary concentrations and brief description of 12 cannabinoids and cannabinoid-metabolites (ng/mL) among 103 eligible participants in Healthy Start

Cannabinoid	Abbreviation	Brief description	n (% detected)	Mean ± SD	Min	Max
Δ9-tetrahydrocannabinol	THC	-Most abundant cannabinoid -Partial agonist of CB_1 and CB_2 receptors in brain, pancreas, and adipose tissue -Fetal exposure associated with β-cell apoptosis	5 (5%)	0.4 ± 0.2	0.3	0.9
11-hydroxy-Δ9-tetrahydrocannabinol	11OH-THC	-Primary metabolite of THC	1 (1%)	0.8	-	-
11-nor-delta 9-carboxy-tetrahydrocannabinol	THC-COOH	-Secondary metabolite of THC	9 (9%)	5.2 ± 6.2	0.3	17.6
Δ9-tetrahydrocannabinol-9-carboxylic acid glucuronide	THC-C-gluc	-Glucuronidated THC-COOH	12 (12%)	214.7 ± 316.2	0	779.8
Δ9-tetrahydrocannabinol glucuronide	THC-gluc	-Glucuronidated THC	8 (8%)	3.8 ± 4.0	0.4	12.0
Cannabidiol	CBD	-Second most abundant cannabinoid -Modulates effects of THC -Low affinity for CB_1 and CB_2 receptors	5 (5%)	0.6 ± 0.1	0.4	0.7
Cannabidiol glucuronide	CBD-gluc	-Glucuronidated CBD	1 (1%)	1.0	-	-
Cannabichromene	CBC	-Agonist of TRPA1 receptors -Anti-inflammatory effects	1 (1%)	0.7	-	-
Cannabinol	CBN	-Mildly psychotropic cannabinoid	0	-	-	-
Cannabigerol	CBG	-Antagonist of CB_1 receptors	2 (2%)	0.3 ± 0.2	0.2	0.5
Δ9-tetrahydrocannabivarin	THCV	-Partial agonist of CB_2 receptors -Antagonizes CB agonists (eg, THC)	1 (1%)	0.7	-	-
Cannabidivarin	CBDV	-Homolog of CBD	0	-	-	-

Abbreviations: CB_1, cannabinoid type 1; CB_2, cannabinoid type 2.

Table 3. Fetal exposure to cannabis[a] and childhood adiposity in Healthy Start, n = 103

				Adjusted means and beta coefficients		
Cannabis categories	n	Fat mass (kg)	Fat-free mass (kg)	Adiposity (% fat mass)	BMI (kg/m^2)	BMI *z*-score
Model 1, n = 103[b]						
Not exposed	88	3.5 (3.2-3.7)	14.2 (13.8-14.6)	19.2 (18.0-20.5)	15.7 (15.2-16.3)	0.0 (-0.3 to 0.2)
Exposed	15	0.7 (0.2-1.2); $P = 0.01$	1.1 (0.3-1.9); $P < 0.01$	1.9 (-0.6 to 4.4); $P = 0.13$	-0.3 (-1.8 to 1.2); $P = 0.65$	0.1 (-0.5 to 0.7); $P = 0.77$
Model 2, n = 90[c]						
Not exposed	78	3.4 (3.2-3.7)	14.1 (13.7-14.6)	19.3 (18.0-20.6)	15.7 (15.2-16.4)	-0.6 (-0.3 to 0.2)
Exposed	12	1.0 (0.3-1.7); $P < 0.01$	1.2 (0.4-2.0); $P < 0.01$	2.6 (0.1-5.2); $P = 0.04$	-0.1 (-1.6 to 1.5); $P = 0.95$	0.3 (-0.3 to 1.0); $P = 0.33$

Abbreviation: BMI, body mass index; LOD, limit of detection.
[a]Fetal exposure to cannabis was determined by the detection of 12 cannabinoids/metabolites of cannabis in maternal urine collected at ~27 weeks' gestation. The categories of were as follows: exposed (any of the measured cannabinoids exceeded the LOD) and not exposed (all of cannabinoids measured were below the LOD).
[b]Model 1 adjusted for maternal age (years), household income (≥$70,000, <$70,000, or missing/declined to answer), maternal race/ethnicity (Hispanic, non-Hispanic Black, non-Hispanic other, and non-Hispanic White), fetal exposure to tobacco (maternal urinary cotinine at ~27 weeks' gestation < LOD, ≥LOD), prepregnancy BMI (kg/m^2), gestational weight gain (kg), offspring sex, gestational age at birth (weeks), birthweight (g), and child age at follow-up visit (years).
[c]Model 2 adjusted for model 1 covariates, as well as the duration of exclusive breastfeeding (breast milk-months) and childhood exposure to secondhand smoke (urinary cotinine < LOD, ≥LOD).

Table 4. Fetal exposure to cannabis[a] and childhood metabolic outcomes in Healthy Start, n = 88

		Adjusted means and beta coefficients		
Cannabis categories	n	Fasting glucose (mg/dL)	Fasting insulin (uU/mL)	HOMA-IR (insulin × glucose/405)
Model 1, n = 88[b]				
Not exposed	75	81.9 (79.8-84.1)	5.6 (5.0-6.2)	1.2 (1.0-1.3)
Exposed	13	8.0 (0.1-15.8); $P = 0.04$	4.0 (0.7-7.3); $P = 0.02$	0.9 (-0.1 to 1.9); $P = 0.08$
Model 2, n = 75[c]				
Not exposed	67	81.5 (79.6-83.3)	5.6 (5.0-6.2)	1.2 (1.0-1.3)
Exposed	8	5.6 (0.8-10.3); $P = 0.02$	2.2 (-0.4 to 4.8); $P = 0.10$	0.3 (-0.2 to 0.9); $P = 0.18$

Abbreviations: BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; LOD, limit of detection.
[a]Fetal exposure to cannabis was determined by the detection of 12 cannabinoids/metabolites of cannabis in maternal urine collected at ~27 weeks' gestation. The categories of were as follows: exposed (any of the measured cannabinoids exceeded the LOD) and not exposed (all of cannabinoids measured were below the LOD).
[b]Model 1 adjusted for maternal age (years), household income (≥$70,000, <$70,000, or missing/declined to answer), maternal race/ethnicity (Hispanic, non-Hispanic Black, non-Hispanic other, and non-Hispanic White), fetal exposure to tobacco (maternal urinary cotinine at ~27 weeks' gestation < LOD, ≥LOD), prepregnancy BMI (kg/m^2), gestational weight gain (kg), offspring sex, gestational age at birth (weeks), birthweight (g), child age at follow-up visit (years), and childhood BMI *z*-scores.
[c]Model 2 adjusted for model 1 covariates, as well as duration of exclusive breastfeeding (breast milk-months) and childhood exposure to secondhand smoke (urinary cotinine <LOD, ≥LOD).

The associations between fetal exposure to cannabis and fat mass, fat-free mass, and adiposity in early childhood were attenuated when we restricted our models to those with information about childhood diet and physical activity levels (n = 103; results not presented). The association between fetal exposure to cannabis and childhood glucose remained statistically significant when we restricted our models to those with information about childhood diet and physical activity levels (n = 56; mean difference: 8.4 mg/dL; 95% CI, 0.8-16.0; $P = 0.03$) but was attenuated following adjustment for these covariates (n = 56; mean difference: 6.4 mg/dL; 95% CI, -1.7 to 14.4; $P = 0.12$) (results not presented).

Discussion

Our findings suggest that fetal exposure to cannabis is associated with increased adiposity and fasting glucose levels in early childhood. Our results were robust and stable, even among our small sample size and after adjusting for relevant confounders. This novel discovery may have important implications given the rise of legalization of cannabis and its use among pregnant women.

Very little is known about the metabolic effects of cannabis. Experimental studies from the 1970s demonstrated that IV administration of THC induced glucose intolerance in healthy adult volunteers (14, 15). More recently, cannabis use has been linked to increased abdominal visceral fat (16), insulin resistance (16), and incident prediabetes (17), as well as an increased risk for diabetic ketoacidosis in adults with type 1 diabetes (18). Conversely, other studies report that cannabis use is associated with similar (19) or lower (20) BMI, lower fasting insulin (21), and a lower prevalence of type 2 diabetes (22) and metabolic syndrome (23).

Our findings suggest a cascade of metabolic effects that may be attributed to fetal exposure to cannabis. Fetal exposure to cannabis was associated with increased adiposity

in early childhood, which is often accompanied by glucose intolerance and insulin resistance (24). Indeed, we observed that fetal exposure to cannabis was associated with higher fasting glucose and insulin levels but not HOMA-IR, which reflects insulin sensitivity in the child (11). This finding may suggest that fetal exposure to cannabis contributes to higher fasting glucose levels via a direct effect on the pancreatic β cells (25). However, we cannot draw conclusions about β-cell response to glucose because we did not perform oral glucose tolerance tests (26).

Contrary to our findings, Cajachagua-Torres and colleagues (9) found no association between maternal or paternal cannabis use during pregnancy with nonfasting glucose among the 10-year-old offspring in the Generation R study. However, this discrepancy could be explained by differences in outcome assessment. The Generation R study measured nonfasting glucose in blood samples collected at different time points in the day, whereas Healthy Start measured glucose in the blood samples collected in the morning after an overnight fast.

The endocannabinoid system may play a mechanistic role in these associations. The endocannabinoid system is made up of 2 receptor types: cannabinoid type 1 (CB_1) and type 2 (CB_2) receptors, along with endogenous cannabinoids and enzymes for biosynthesis of these cannabinoids. CB_1 receptors are abundant in the brain (27), including in the hypothalamus (responsible for energy metabolism, fuel storage, and appetite regulation). CB_1 and CB_2 receptors are also found in adipose tissue (25) and insulin-producing β cells and glucagon-producing α cells (28). In a healthy fetus, CB_1 and CB_2 receptors are modulated by endogenous cannabinoids (29). However, fetal exposure to cannabis may disrupt molecular control of insulin and glucagon release (30).

There is a need to understand the relative contribution of the individual cannabinoids of cannabis, given their distinct and sometimes opposing effects. For instance, THC acts as a partial agonist of CB_1 and CB_2 receptors (27). Conversely, CBD is capable of antagonizing CB_1 receptor agonists (eg, THC), which explains its well-documented counteractive effects of THC (27). Our study incorporated 12 cannabinoids and metabolites of cannabis. As expected, THC-gluc, THC-C-gluc, and THC-COOH were the most readily detectable metabolites in our study (10). This is intuitive, given that THC is the most abundant cannabinoid in cannabis and its metabolites are extremely lipophilic. On the other hand, the other 6 cannabinoids (THCV, CBD, CBC, CBN, CBG, and CBDV) were only detected in a sparse number of women. This prohibited our ability to investigate each individual cannabinoid, which represents an important gap that should be explored in future studies.

Our results are strengthened by the objective measurement of fetal exposure to cannabis by urinalysis, which may provide a more accurate representation of the true burden of this exposure. However, mothers in our study were not asked to self-report cannabis use or exposure during pregnancy. Furthermore, cannabinoids were only measured at 1 time point during pregnancy, with no assessment of exposure during the postnatal period. Therefore, we were unable to differentiate maternal active use from secondhand exposure to cannabis during pregnancy or assess sensitive windows.

The direct measure of fat mass, fat-free mass, and adiposity in childhood is another strength of our approach. We found that fetal exposure to cannabis was associated with the direct measures of body composition, especially adiposity (fat mass percentage) in fully adjusted models, but not with BMI and BMI *z*-scores. The use of air displacement plethysmography likely reduced measurement error of childhood adiposity in our study. Furthermore, differences in the assessment of body composition could explain why some studies have reported that active cannabis use among adults is associated with similar (19) or lower (20) BMI, whereas others report increased abdominal visceral fat (as measured by magnetic resonance imaging) (16).

Although we adjusted for many important covariates (including fetal and childhood exposure to tobacco and childhood BMI *z*-scores) and observed little impact on our results, there is potential for residual confounding. For instance, a previous study found that self-report of cannabis use during pregnancy is associated with a shorter duration of exclusive breastfeeding (4), whereas we observed little difference in the duration of exclusive breastfeeding between exposed and nonexposed groups. Mothers may have overreported the duration of exclusive breastfeeding because of social desirability (31). Furthermore, because of our restricted sample size, we were unable to adjust for important confounders (such as childhood diet and physical activity) in our main analyses.

Conclusions

The potential risks associated with cannabis use during pregnancy have not been as widely communicated as the deleterious effects of tobacco use during pregnancy. Furthermore, cannabis use is growing in popularity and acceptance among pregnant women. Between 2002 and 2016, self-reported use of tobacco among pregnant women, ages 18 to 44 years, decreased (17.5% to 10.3%) whereas self-reported use of cannabis increased (2.9% to 5.0%) (32). The prevalence of use is likely to be even higher, especially among younger women (1) or in states with fully legalized cannabis (33). There is a rapidly expanding body of research dedicated to understanding the potential impact of cannabis use during pregnancy on the offspring. Here, we provide novel evidence to suggest an association between fetal exposure to cannabis and increased adiposity and fasting glucose levels in early childhood, a finding needs to be validated in other cohorts. Nevertheless, women should be discouraged from using any cannabis while pregnant or breastfeeding to minimize adverse health effects of the offspring.

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Conflict of Interest

None declared.

Data Availability

The dataset analyzed in this study is protected under an institution review board protocol and is not available for distribution.

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