Prenatal Substance Exposure and Birth Weight: Findings From the HEALthy Brain and Child Development Study

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abstract

OBJECTIVE: To estimate associations of more than minimal prenatal nicotine, alcohol, cannabis, and opioid exposures with gestational age, birth weight, and birth weight for gestational age.

METHODS: Data were drawn from the HEALthy Brain and Child Development (HBCD) Study, a multisite, longitudinal study in the United States. Predefined recruitment thresholds for each substance were assessed using maternal self-report, maternal toxicology results, and newborn substance exposure-related diagnoses. Birth outcomes included gestational age at delivery (weeks), birth weight (grams), and birth weight for gestational age (centiles). Mean differences and risk ratios for the associations between substance exposure and birth outcomes were estimated using multilevel mixed-effect linear regression or multilevel mixed-effect Poisson regression.

RESULTS: Among 660 mother-infant dyads, 17% (n = 115) of participants met recruitment thresholds for prenatal cannabis, 15% for nicotine (n = 102), 13% for alcohol (n = 86), and 5% for opioids (n = 32). In adjusted models, prenatal cannabis and opioid exposures were each associated with lower birth weight (cannabis: −272.2 [95% CI −444.6 to −99.8] g; opioids: −295.4 [95% CI −574.9 to −15.9] g) and birth weight centiles (cannabis: −8.2 [95% CI −15.3 to −1.1] centiles; opioids: −14.4 [95% CI −25.5, −3.4] centiles), although the results were sensitive to model specifications. Prenatal nicotine and alcohol estimates were in similar directions but not statistically significant. No significant associations between exposures and gestational age at delivery were detected.

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WHAT'S KNOWN ON THIS SUBJECT: Prenatal substance use during pregnancy is highly prevalent but its potential impact on offspring outcomes remains poorly understood. Large, well-characterized datasets with both self-report and toxicology are necessary to fully characterize and analyze prenatal substance exposure.

WHAT THIS STUDY ADDS: Our findings of an association between both cannabis and opioid exposures and birth size add to an inconsistent literature. Future studies from this growing cohort can confirm and expand findings into childhood outcomes.

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CONCLUSIONS: In this initial HBCD Study data release, more than minimal exposure to cannabis and opioids was associated with smaller birth size, adding evidence to an inconsistent literature. Future studies from HBCD can more deeply interrogate timing and dose of each substance and expand to childhood outcomes.

INTRODUCTION

In the United States, approximately 20% of pregnancies involve substance exposure,[1] most commonly nicotine (8%–11%), alcohol (7%–10%), and cannabis (4%–8%).[1–3] Among pregnant individuals with substance use, polysubstance use is common.[3] Fetal exposure to substances has been linked with a variety of physical and behavioral health outcomes.[4,5] Some of the earliest reported associations of prenatal substance exposure are shorter gestations and lower birth weight or size-for-gestational age,[6–13] factors also known to be associated with later negative neurodevelopmental functioning in children.[14–16] However, findings related to prenatal substance exposure and adverse birth outcomes are limited and inconsistent,[17–20] leading to uncertainty about risks for pregnant individuals and clinicians.[21–25] Inconsistent results are often caused by small sample sizes; reliance on recall and self-report; limited adjustment for maternal factors, including co-use of other substances; and limited data on dose, timing, and duration of substance exposure.[26–29]

To characterize associations of prenatal substance exposure, large prospective studies that collect detailed information on substance exposure during gestation are needed. The HEALthy Brain and Child Development (HBCD) Study is the largest US study of brain development from birth into middle childhood.[5] The HBCD Study protocol, described in detail elsewhere,[4,5,30–44] establishes the type of deeply phenotyped data currently lacking to elucidate relationships between prenatal substance exposure and early childhood outcomes. The study began recruitment in 2023 with the goal of recruiting a generally representative sample of more than 7000 pregnant individuals and their offspring followed through the first decade of life.

To coincide with the first public release of HBCD data and add well-characterized, prospectively collected evidence to the existing literature on prenatal substance exposure and birth outcomes, we examined associations of more than minimal nicotine, alcohol, cannabis, and opioid exposures with gestational age, birth weight, and birth weight for gestational age. By highlighting protocol elements pertaining to prenatal substance use and providing analytic code, this article may guide future investigators analyzing HBCD data on prenatal substance exposures and childhood outcomes.

METHODS

Study Design

Each of 27 recruitment sites enrolled a pregnant sample from their site's catchment area,[5] relying on diverse methods including social media platforms, obstetric clinics, and substance use treatment facilities.[31] Per protocol,[5] participants were enrolled in the second or third trimester of pregnancy. Inclusion criteria were English- or Spanish-speaking pregnant individuals aged at least 18 years; exclusion criteria were any plan to terminate the pregnancy or not to retain custody of the child. To ensure sufficient exposure to study opioids, alcohol, cannabis, and nicotine/tobacco, the study was designed for at least 25% of the sample to have more than minimal prenatal substance use (12% each exposure accounting for co-use between groups). Other substances were queried but were not specified in recruitment targets.

The HBCD Study releases cumulative data annually. Data for this analysis were drawn from the HBCD 1.0 data release, which included all visits completed by July 1, 2024. The resulting sample contained 1426 participants with a prenatal visit 1 (V1: maternal health and substance use, biospecimens) and 660 with a visit 2 (V2: 0–1 months postdelivery, pregnancy and birth outcomes). Additional details on study measures are available in prior papers,[4,5,30–42] the study website (http://www.HBCDstudy.org), and the data documentation website (https://docs.hbcdstudy.org/latest/).

All adult participants consented for themselves and their children, and the study was approved by a single institutional review board (IRB) in addition to the IRBs of all involved institutions. Fully de-identified data were obtained through the National Institute of Health Brain Development Cohorts Data Hub (https://www.nbdc-datahub.org/) under an institutional data use certification.

Exposures, Outcomes, and Covariates

Prenatal substance exposure classification was based on self-report, biospecimens, and infant substance-related diagnoses as follows. At V1, individuals self-reported substance use using the National Institute on Drug Abuse–modified ASSIST,[45] expanded for the HBCD Study from 9 to 18 substances.[4] Participants with reported substance use in the 3 months before or during pregnancy were subsequently interviewed by trained research staff about the timing and frequency of use using a timeline follow-back (TLFB) method.[46] The TLFB asked about substance use each day for each endorsed substance for 5 weeks during

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pregnancy: 4 early weeks of pregnancy (last menstrual period [LMP] + 2 weeks through LMP + 6 weeks) and the week before enrollment. At V2, participants reported whether they used substances between their prenatal visit (V1) and delivery; an endorsement was followed by a TLFB interview to collect daily substance use for each endorsed substance during the last 2 full weeks of gestation. In addition, all participants (regardless of substance use report) were asked to provide a urine sample (V1) and nail clippings (V1 and V2) for toxicology, and at V2 reported any infant diagnoses of fetal alcohol syndrome (FAS; alcohol) or neonatal opioid withdrawal syndrome (NOWS; opioids). From the 7 weeks of self-reported substance use on the TLFB, toxicology, and maternal-reported FAS and NOWS diagnoses, participants were categorized into each exposure group when they met or exceeded threshold definitions (as defined in Table 1).[4] Individuals not meeting substance exposure thresholds and with negative toxicology results were included in the general population sample.

Birth outcomes were assessed as both continuous and categorical variables. Gestational age (in floored gestational weeks) from maternal report was calculated from the birth date minus the study-calculated LMP (expected due date − 40 weeks). Preterm birth (dichotomous) was defined as less than 37 completed gestational weeks. Low birth weight (LBW; dichotomous) from maternal report was defined as birth weight less than 2500 g. Sex-specific birth weight for gestational age centiles were calculated using Intergrowth curves.[47] Small for gestational age (dichotomous) was defined as birth weight less than the 10th percentile for gestational age and sex.

TABLE 1. Thresholds of Prenatal Exposure Used to Assess Enrollment Goals for the HEALthy Brain and Child Development Study

Exposure	Thresholds
Opioid use	Any self-reported use of prescribed (including medications for opioid use disorder) or illicit opioids for ≥2 weeks during pregnancy in the timeline follow-back OR
	Diagnosis with neonatal opioid withdrawal syndrome OR
	Positive toxicology for an opioid for research-collected biospecimen
Alcohol use	Any self-reported use equal to ≥7 standard drinks per week for ≥2 weeks during pregnancy in the timeline follow-back OR
	Any self-reported use equal to ≥3 standard drinks per occasion on ≥2 occasions during pregnancy in the timeline follow-back OR
	Diagnosis with fetal alcohol syndrome OR
	Positive toxicology for alcohol for research-collected biospecimen
Cannabis use	Any self-reported use of cannabis for ≥4 weeks during pregnancy in the timeline follow-back OR
	Positive toxicology for cannabis for research-collected biospecimen
Nicotine/ nicotine use	Any self-reported use of nicotine or nicotine products for ≥4 weeks during pregnancy in the timeline follow-back OR
	Positive toxicology for nicotine for research-collected biospecimen

Used with permission from Gurka et al.[4]

Covariates for adjustment were selected based on hypothesized associations with prenatal substance exposure and birth outcomes. Covariates included self-reported maternal race and ethnicity (non-Hispanic white, non-Hispanic Black, Hispanic, or other race [Asian, American Indian/Alaska Native, or 2 or more races]), age at delivery (years), gravidity (number of pregnancies, including current pregnancy), self-reported maternal education (dichotomized at high school diploma or equivalent vs above), health insurance payer (private, public, other source of insurance, or no insurance), Supplemental Nutrition Program for Women, Infants, and Children (WIC) benefits receipt (yes/no), and maternal depression (measured with the total score of the Edinburgh Postnatal Depression Scale [EPDS]),[48] all collected at V1. Although race and ethnicity are social constructs, they were included in analytic models, along with age and proxies for income, because of the documented disparities among minority, young, and lower-income individuals in the receipt of substance use treatment[49,50] and in adverse birth outcomes,[51] both likely because of structural factors.

Statistical Analysis

Exposure was dichotomized at or above enrollment thresholds compared with below thresholds or no substance use for analysis. Analytic code to classify exposure thresholds is referenced in the Supplemental Materials. Mean differences for associations between prenatal substance exposure and continuous birth outcomes were estimated using multilevel mixed-effect linear regression with a random effect for the study site. Adjusted models were specified in 2 ways. Adjusted mean differences were first estimated using the same linear regression model with the addition of inverse probability of treatment weighting (IPTW) to account for the effect of covariates. Models were then repeated with multivariable adjustment with the same covariates. The 4 substances were included in the same model to estimate associations independent of each other. Risk ratios for associations between prenatal substance exposure and binary birth outcomes were estimated using a multilevel mixed-effect Poisson regression with a robust variance estimator and study site as a random effect. Adjusted risk ratios were estimated using the same Poisson model with the addition of IPTW and were also repeated with multivariable adjustment. The estimation of inverse probability weights has been described previously[52] and is detailed in the Supplemental Materials. In a sensitivity analysis, the

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reference group for each substance was disaggregated into no exposure and exposure below the thresholds, with no exposure serving as the reference group in multivariable adjusted models. Complete case analysis was performed for all models (5% missing overall in sample). Cell sizes under 11 were suppressed. All analyses were performed in Stata SE 18.5.

RESULTS

There were 660 participants included in the analytic sample from HBCD 1.0 (Figure 1). The sample was predominantly non-Hispanic white (51%) followed by non-Hispanic Black or African American (21%) (Table 2). Most participants had postsecondary education (81%) and private insurance (60%); 24% of participants used WIC benefits, and 10% had EPDS scores indicating probable depression (≥13).[48] Individuals who met prenatal substance exposure criteria were more likely to identify as non-Hispanic Black or African American, be insured through Medicaid, receive WIC benefits, screen positive for probable or possible depression on the EPDS, and were less likely to have education beyond a high school diploma. Characteristics by each substance are listed in Supplemental Table 2.

Substance Use

Prenatal substance exposure criteria were met by 17% of participants for cannabis (n = 115), followed by nicotine (15%; n = 102), alcohol (13%; n = 86), and opioids (5%; n = 32) (Table 2); 432 (65%) did not meet the criteria for any of the 4 exposures. The specific criteria (self-report, toxicology, or infant diagnoses) that determined prenatal substance exposure status varied by substance (Supplemental Figures 1–4). For alcohol, the most common source was self-report alone (88%). For cannabis, the most common sources were self-report, nail and urine toxicology (30%), and nail toxicology alone (19%). For nicotine, the most

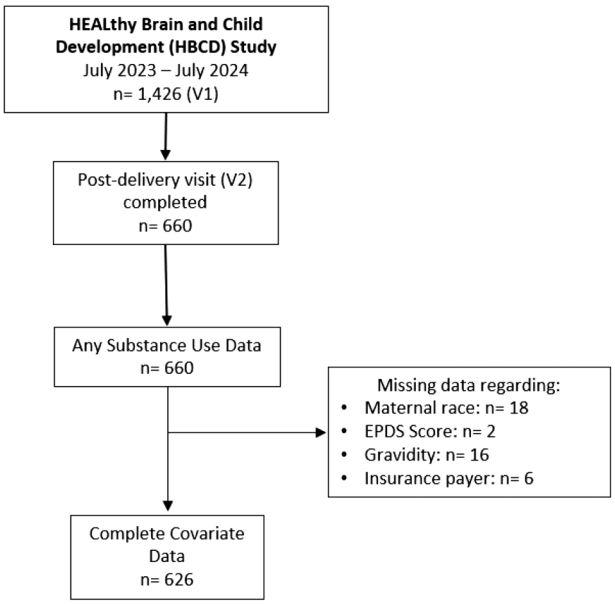


FIGURE 1.
Cohort selection of completed visits eligible for inclusion in the HBCD data release 1.0.
Abbreviations: EPDS, Edinburgh Postnatal Depression Scale; HBCD, HEALthy Brain and Child Development.

TABLE 2. Description of the HEALthy Brain and Child Development Study Cohort (Release 1.0), by Any Substance Use

	Total	None or Below Threshold Substance Use	At or Above Threshold Substance Use
	N = 660	n = 432	n = 228
Substance use parameters, n (%)			
Alcohol (any source)	86 (13)	0 (0)	86 (38)
Cannabis (any source)	115 (17)	0 (0)	115 (50)
Nicotine (any source)	102 (15)	0 (0)	102 (45)
Opioids (any source)	32 (5)	0 (0)	32 (14)
Maternal and pregnancy characteristics			
Maternal race, n (%)			
Non-Hispanic white	338 (51)	244 (56)	94 (41)
Non-Hispanic Black or African American	136 (21)	60 (14)	76 (33)
Hispanic	82 (12)	58 (13)	24 (11)
Other race (includes >1 race)	86 (13)	60 (14)	26 (11)
Maternal age at delivery, median (IQR), y	33 (29–36)	33 (30–36)	31 (26–34)
Number of pregnancies, median (IQR)	2 (1–4)	2 (1–3)	2 (1–4)
Maternal education (more than a high school diploma), n (%)	537 (81)	389 (90)	148 (65)
Insurance payer, n (%)			
Private	395 (60)	317 (73)	78 (34)
Medicaid	159 (24)	61 (14)	98 (43)
Other (eg, Tricare, Healthcare.gov, and Indian Health Service)	71 (11)	40 (9)	31 (14)
No insurance	29 (4)	12 (3)	17 (7)
Supplemental Nutrition Program for Women, Infants, and Children, n (%)	159 (24)	67 (16)	92 (40)
Possible depression (EPDS ≥9), n (%)	158 (24)	81 (19)	77 (34)
Probable depression (EPDS ≥13), n (%)	68 (10)	33 (8)	35 (15)
EPDS score, median (IQR)	5 (2–8)	4 (2–7)	5 (3–10)
Infant sex (male), n (%)	335 (51)	224 (52)	111 (49)

Abbreviation: EPDS, Edinburgh Postnatal Depression Scale.

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common sources were self-report, nail and urine toxicology (34%), and urine toxicology alone (18%). For opioids, the predominant sources were self-report and nail and urine toxicology (41%).

We also examined single vs polysubstance prenatal exposure (Supplemental Figure 5). The most common single prenatal substance exposure was alcohol alone (10%; n = 60) followed by cannabis alone (7%; n = 45). The most common prenatal polysubstance exposure was a combination of nicotine and cannabis (6%; n = 40). Additional combinations of substance exposure by substance are described in the Supplemental Materials. Generally, alcohol was the substance most likely to be used alone, and nicotine was the least likely substance to be used alone.

Infant Outcomes

Gestational Age at Delivery

The median gestational age at delivery was 39 (IQR, 38–40) weeks. In unadjusted and adjusted models, point estimates for the 4 exposures signaled a reduction in completed gestational weeks but were not statistically significant (Figure 2; Supplemental Table 3). Eight percent (n = 53) of the sample were born prematurely. In models for preterm birth (Supplemental Table 4), there were no statistically significant associations.

Birth Weight

The median weight at birth was 3260 (IQR, 2920–3600) g. In unadjusted models, each substance exposure was associated with lower birth weight, although alcohol exposure was not statistically significant (Figure 3; Supplemental Table 3). In adjusted models, opioid and cannabis exposure remained significantly associated with reduced birth weight, although cannabis estimates were sensitive to model specification. Eight percent (n = 52) of the sample was LBW. In models for LBW (Supplemental Table 4), none of the exposures were statistically significant.

Birth Weight for Gestational Age

The median birth weight for gestational age was 65th percentile (IQR, 38–86). Opioid, cannabis, and nicotine exposures were significantly associated with reductions in birth weight for gestational age, whereas estimates for alcohol exposure were not (Figure 4; Supplemental Table 3). After adjustment, cannabis and opioid exposure remained negatively associated with birth weight for gestational age centile, whereas estimates for nicotine exposure were attenuated. Five percent (n = 32) of the sample were small for gestational age at birth. In models for small for gestational age (Supplemental Table 4), there were no significant associations.

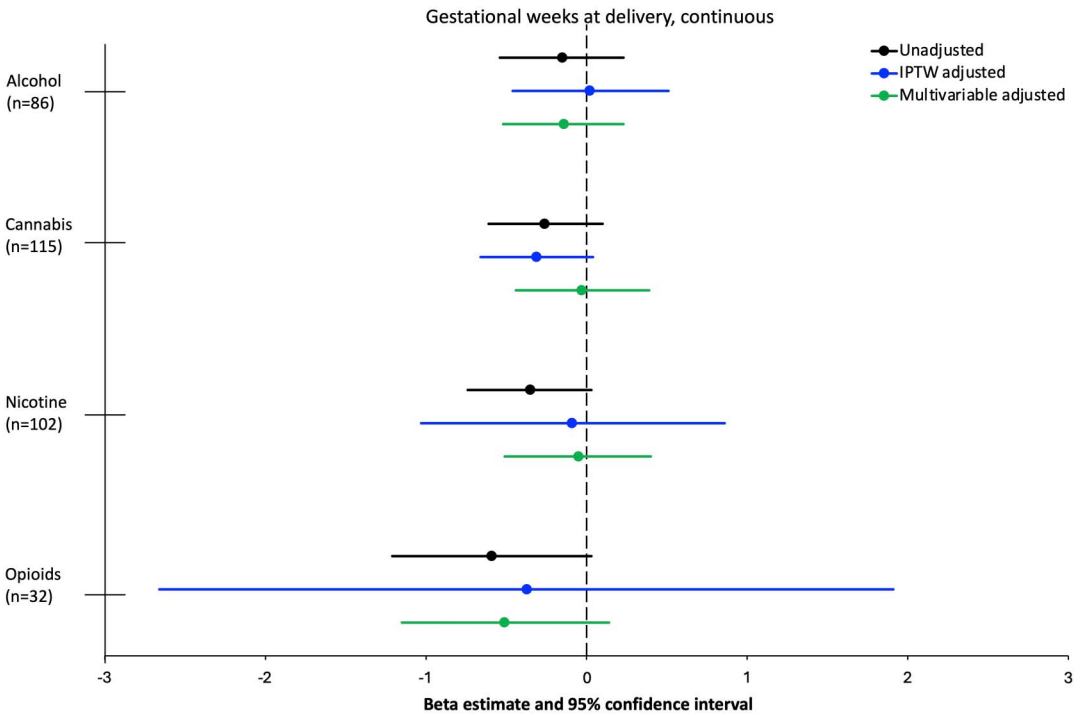


FIGURE 2.
Beta estimates for substance exposure and gestational weeks at delivery. Adjustment via IPTW (blue) and multivariable adjustment (green). Abbreviation: IPTW, inverse probability of treatment.

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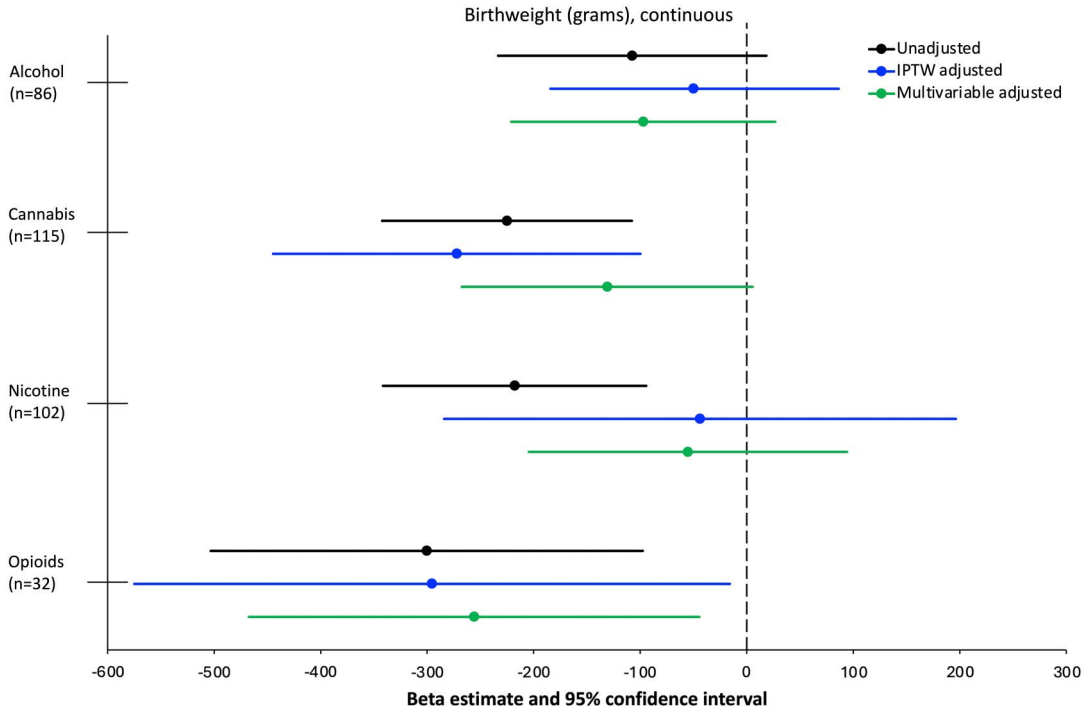


FIGURE 3.
Beta estimates for substance exposure and birth weight. Adjustment via IPTW and random effect for site (blue) and multivariable adjustment and random effect for site (green).
Abbreviation: IPTW, inverse probability of treatment.

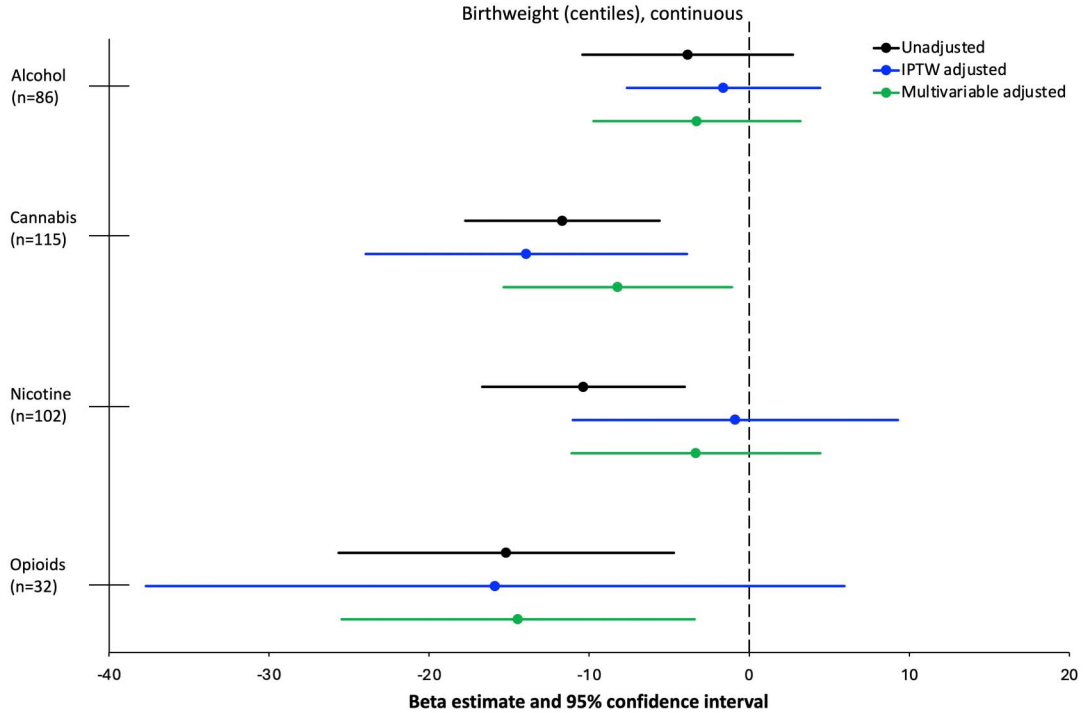


FIGURE 4.
Beta estimates for substance exposure and birth weight centile. Adjustment via IPTW and random effect for site (blue) and multivariable adjustment and random effect for site (green).
Abbreviation: IPTW, inverse probability of treatment.

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Sensitivity Analysis

Most infants in each reference group had no exposure to that substance (negative toxicology result, no report on TLFB, no NOWS/FAS: alcohol: n = 402 [70% of reference group]; cannabis: n = 519 [95%]; nicotine: n = 544 [97%], and opioids: n = 620 [99%]). When the reference group was disaggregated into "no exposure" and "exposure below threshold," results were unchanged when comparing exposure at or above thresholds to no exposure (Supplemental Table 5; Supplemental Figures 6–8). Estimates of exposure falling below thresholds for each substance were null, and typically attenuated relative to estimates of use above the thresholds, although all CIs for the 2 exposure groups overlapped.

Post Hoc Analyses

To test the robustness of the findings, we repeated multivariable linear models for cannabis with exposure limited to positivity from biospecimens (with or without self-report; n = 105 exposed) and separately from self-report (with or without biospecimens; n = 75 exposed) for birth weight and birth weight for gestational age. There was little difference between sources of exposure (Supplemental Table 6; Supplemental Figure 9) for either outcome. There were too few opioid-exposed infants to stratify results by positivity source.

DISCUSSION

In data from the HBCD Study, more than minimal levels of prenatal cannabis and opioid exposure were associated with lower newborn birth weight and birth weight for gestational age. Cannabis findings were robust when examined by source of exposure (toxicology vs self-report). Estimates from nicotine and alcohol models were not statistically significant. These findings are relevant given the inconclusive literature and uncertainty among pregnant individuals and clinicians regarding select prenatal substance exposures, particularly cannabis.[21–25]

In our US birth cohort study, participants met the exposure thresholds for common substances, including cannabis (17%), nicotine (15%), alcohol (13%), and opioids (5%). Because of oversampling for opioids[53,54] and the use of thresholds to define "more than minimal" substance exposure, HBCD prenatal substance exposure estimates are not directly comparable with substance use rates in population-based samples like the National Survey on Drug Use and Health[1] or Pregnancy Risk Assessment Monitoring System.[3] However, HBCD prevalence estimates by information source are informative to other studies, as most data collection relies on self-report. Although more than 90% of alcohol use in HBCD was captured with self-report, only 66% of cannabis, 62% of nicotine, and 72% of opioids were captured by self-report (data not fully shown because of cell suppression). The prevalence discordance between sources was expected; toxicology classified any positive result as exposed, whereas self-report required meeting use thresholds, and urine, fingernail, and toenail specimens vary in toxicology lookback periods.[55] Nevertheless, this approach likely provides more inclusive exposure ascertainment, and future work should continue to analyze whether findings differ by source.

In the HBCD sample, co-use of the 4 substances was common. Although alcohol was primarily used alone, most who used nicotine, cannabis, and opioids also met criteria for at least 1 other substance. These findings underscore the importance of considering co-exposure in clinical care and research.

Our findings with respect to birth outcomes were nuanced. All 4 substances of interest have been associated with lower gestational age, birth weight, and birth weight for gestational age in prior studies,[9–11,13,56] although the literature is inconsistent and many studies are noted as having low methodological quality.[17–20] In our models, many findings attenuated upon adjustment, reflecting confounding common in studies of prenatal substance exposure. Nicotine models appeared most affected by confounding, which in post hoc analyses were largely driven by race and ethnicity, education, and depression. In addition, approximately 40% of participants with self-reported nicotine had discontinued use by enrollment (data not shown), potentially minimizing the strength of associations with birth outcomes.[57] For all substances, our imprecise estimates are also a function of exposure definitions, as predefined exposure levels reflect more than minimal use, which may include lower levels of use relative to other prenatal exposure studies. Further, substances were aggregated across types (eg, opioid exposure consists of medications for opioid use disorder (OUD) and prescription and nonprescription products), which increases heterogeneity in estimates.

Although the analytic sample for the HBCD Study will continue to grow over the next several years, these early findings may contribute to prenatal counseling. Misperceptions of cannabis as "natural" or "safe" persist, and studies note a lack of clear information or communication about cannabis-related risks.[58,59] Our findings support public health messaging and clinical recommendations to discontinue cannabis use in pregnancy.[60] Moreover, our findings on opioids and lower birth weight may assist clinicians and pregnant people when preparing for opioid-exposed births. Notably, prenatal agonist medication treatment of OUD is an evidence-based approach, with documented reductions in maternal morbidity and mortality and improved birth outcomes. This analysis was unable to separate medications for OUD (n = 17) from other opioid exposures (n = 16, with overlap between the 2) because of the small sample size and also could not consider timing of treatment initiation. As the HBCD sample grows, those analyses may be possible.

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These findings should be viewed considering study limitations. Although each site attempted to enroll a generally representative sample from their catchment area, recruitment denominators were not captured and representativeness cannot be determined. These initial findings from the first HBCD data release are based on less than 10% of the anticipated final sample size of the HBCD Study, resulting in imprecise estimates and models that were sensitive to model specifications. In addition, we did not assess the mode of use (eg, vaping vs edibles), type of use (eg, opioid-agonist medication treatment vs nonprescription opioids), dose, timing, duration, or joint effects of exposures, although this information will be available in future data releases. Additionally, although the HBCD Study recruitment design specified these 4 relatively common prenatal exposures, the study is collecting detailed information on 18 substances, including stimulants, which have increased in use.[61–63] The prevalence of remaining exposures remains low, and we did not include other exposures because of small cell sizes. This may have resulted in biased estimates. It is also possible that some prenatal substance exposure was misclassified. To minimize participant burden and potential recall bias, only 7 weeks of pregnancy were queried on TLFB interviews,[4] and toxicology has variable lookback periods.[55] Both could lead to misclassification of exposure, potentially attenuating results. It should be noted, however, that the combination of the TLFB interviews and biomarkers assessed in both maternal urine and nail clippings is one of the most comprehensive in the field. Additionally, although beyond the scope of this analysis, future analyses can look at maternal nutrition as a mediator and modifier of the relationship between prenatal substance exposure and birth outcomes, which has previously been documented.[64] Finally, we relied on maternal report of birth weight and length of gestation, which may have resulted in misclassification and should be validated in future data releases when medical record data are available.

In conclusion, we found that prenatal cannabis and opioid exposures were each associated with smaller birth size. These findings align with existing recommendations to abstain from cannabis in pregnancy and support the need for disaggregated analyses of opioid exposure.

ABBREVIATIONS

EPDS: Edinburgh Postnatal Depression Scale
FAS: fetal alcohol syndrome
HBCD: HEALthy Brain and Child Development
IPTW: inverse probability of treatment weighting
IRB: institutional review board
LBW: low birth weight
LMP: last menstrual period
NOWS: neonatal opioid withdrawal syndrome
OUD: opioid use disorder
TLFB: timeline follow-back
V1: visit 1
V2: visit 2
WIC: Women, Infants, and Children

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