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Latent Class Analysis of Prenatal Substance Exposure and Child Behavioral Outcomes

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Abstract

Objectives: To predict behavioral disruptions in middle childhood, we identified latent classes of prenatal substance use.

Study Design: As part of the Environmental influences on Child Health Outcomes (ECHO) Program, we harmonized prenatal substance use data and child behavior outcomes from 2,195 women and their 6- to 11-year-old children across 10 cohorts in the United States and used latent class–adjusted regression models to predict parent-rated child behavior.

Results: Three latent classes fit the data: low use (90.5%; n=1,986), primarily using no substances; licit use (6.6%; n=145), mainly using nicotine with a moderate likelihood of using alcohol and marijuana; and illicit use (2.9%; n=64), predominantly using illicit substances along with a moderate likelihood of using licit substances. Children exposed to primarily licit substances in utero had higher levels of externalizing behavior than children exposed to low or no substances (p=.001, d=.64). Children exposed to illicit substances in utero showed small but significant elevations in internalizing behavior than children exposed to low or no substances (p<.001, d=.16).

Conclusions: The differences in prenatal polysubstance use may increase risk for specific childhood problem behaviors; however, child outcomes appeared comparably adverse for both licit and illicit polysubstance exposure. We highlight the need for similar multi-cohort, large-scale studies to examine childhood outcomes based on prenatal substance use profiles.

Keywords

Child development; behavior problems; prenatal substance use; latent profile analysis; opioid use

Prenatal substance use continues to be a major public health issue. In the United States, approximately 1 in 5 women report use of legal or illegal substances while pregnant, varying from tobacco and alcohol to psychoactive drugs, such as opioids and cocaine.[1] Women are most likely to use tobacco, alcohol, cannabis, stimulants, and opioids from 18 to 29 years of age, increasing the likelihood of substance use occurring during pregnancy.[2] Furthermore, use of one substance in isolation is infrequent, with upwards of 50% of pregnant women using one substance and reporting use of at least one other substance.[2]

Distinctive combinations of substance use could more negatively impact child outcomes. Yet, limited research has examined whether pregnant women can be categorized based on their substance use. This information is critical to caregivers, clinicians, researchers, and policy makers for the identification of women whose children are most at-risk for neurodevelopmental delay. Co-substance exposures may have augmented effects that are detrimental to the child. The effects may be additive, with children exposed to a higher number of substances in utero having more negative outcomes,[3] or the unique combination of substances may alter the pharmacodynamics. For example, use of cocaine or heroin facilitates the transfer of methadone across the placenta to the fetus, potentially increasing the likelihood of developmental disruptions.[4]

The neurodevelopmental consequences associated with prenatal substance exposure may persist well into childhood, if not further.[5] Children exposed to substances in utero often develop problem behaviors, which can impair academic performance and negatively impact mental health.[6] Prenatal exposures to alcohol,[7,8] tobacco,[9,10] cocaine,[11,12] opioids,[13] cannabis,[14] and methamphetamine[15] have been individually linked to high levels of externalizing behavior in middle childhood. Fewer studies have found an association between prenatal substance exposure and internalizing behavior. Prenatal opioid exposure has been linked to elevated internalizing behavior,[13] including child anxiety,[16] while in utero exposure to individual substances, such as alcohol and marijuana, have been related to increased child depressive symptoms.[17,18] However, much of the existing research examines the child consequences of individual substance exposures, controlling for other substance exposures or is limited to young children.[13,19]

Few studies have assessed prenatal polysubstance exposure and behavioral outcomes in later childhood.[3,20,21] One study found that 4.5-year-old children prenatally exposed to opioids and polysubstances experienced more regulatory and attention problems than non-exposed peers according to teacher report but not parent report.[20] However, by 8.5 years of age, both teachers and parents reported the same high levels of child behavioral problems, suggesting that the behavioral consequences associated with prenatal substance exposure may become more apparent in middle childhood, theorized to be triggered by cognitive and affective stressors, including age-related expectations to regulate behavior and engage in sustained attention[19,22] and the influences of the caregiving environment.[23,24] Identifying prenatal polysubstance use classes that are strongly related to deleterious childhood outcomes could provide insight into which children may be at higher risk for neurodevelopmental concerns.

Utilizing data from the Environmental influences on Child Health Outcomes (ECHO) Program we 1) identified discrete patterns of polysubstance use during pregnancy, expecting at least two latent subgroups of women to be classified based on their substance use—a low or no substance group and a polysubstance group, and 2) tested the predictive validity of these groups by determining whether they were associated with problem behavior in 6- to 11-year-old children, hypothesizing that children with prenatal polysubstance exposure would have higher levels of externalizing and internalizing behavior problems in middle childhood than those children with little to no prenatal substance exposure.

METHODS

Environmental influences on Child Health Outcomes (ECHO) Program

The ECHO Program consists of 69 existing pediatric cohorts across the United States focusing on five key areas of child health: prenatal, perinatal, and postnatal health; obesity; respiratory conditions, including asthma; neurodevelopment; and positive health/well-being.[25,26] The goal of ECHO is to utilize existing pediatric studies by combining data collected under cohort-specific protocols and data collected using the ECHO-wide cohort data collection protocol[27] (https://echochildren.org/echo-program-protocol/) to investigate the effects of early exposures on child health. The study protocol was approved by the local and/or central ECHO institutional review board. Written informed consent or parent's/guardian's permission was obtained along with child assent as appropriate, for ECHO-wide Cohort Data Collection Protocol participation and for participation in specific cohorts.

Participants

The current study was comprised of 10 ECHO-wide cohorts with information on prenatal substance use and child behavior from 2000–2020 (Table 1; online). The 2,195 women in the study included 54% non-Hispanic/White, 31% non-Hispanic/Black, 2% non-Hispanic/Asian, 6% non-Hispanic/Other, and 8% Hispanic. Pregnant women were, on average, 28 years old at the birth of their child (*SD*=6.2), and 62% of these births occurred from 2000–2010, with the remaining births occurring from 2011–2020.

Prenatal Substance Use

All prenatal substance use data for the current study were ascertained through self-report for any substance use during pregnancy, not accounting for the exact timing and duration (Table 1; online). We created binary variables (yes/no) for nicotine, alcohol, marijuana, opioid, and/or illicit drug use during pregnancy. See Supplementary Materials for definitions of substances.

Child Behavior Outcomes

We used the Child Behavior Checklist (CBCL)—an established and widely used instrument with high validity and reliability[28]—to assess child behavior problems. Caregivers completed the CBCL-School aged version when their children were 6 to 11 years old. The CBCL consists of 113 items related to child behavioral issues scored on a 3-point scale ranging from not true (0) to often true or very true (2). We transformed raw CBCL scores, calculated by summing the corresponding CBCL responses, and determined the externalizing problem score (ie, sum of the rule-breaking and aggressive behavior scores) and the internalizing problem score (ie, sum of the anxious/depressed, withdrawn/depressed, and somatic complaints scores). We used the corresponding sex- and age-standardized t-scores for analysis (M=50, SD=10). T-scores <60 represent a typical range of scores, 60–63 represent borderline scores, and >63 represent scores in the clinical range, indicating higher than average problem behaviors. Externalizing and internalizing behavior t-scores were correlated at .61 (p<.001).

Statistical Analysis

We used multiple imputation for missing data; see Table 2 and Supplementary Materials for more information. We modeled the heterogeneity of prenatal substance use using latent class analysis,[29] which identified underlying patterns within the data to qualitatively group mothers into classes based on their reported substance use during the prenatal period. To determine the number of latent classes, we compared goodness of fit indices using standard fit statistics, including [30–35] We included maternal ethnicity/race, marital status, maternal age at delivery, and maternal education as predictors of class membership. These data were included as predictors because they are considered proxy measures for unmeasured social determinants of health, such as exposure to racial discrimination. We chose the final model (ie, number of classes) that best fit the data, then the model was run without covariates to obtain most likely class membership, which was used in additional models to account for measurement error.[33] Full information maximum likelihood estimation was used to adjust parameter estimates to reflect missingness, and the cluster command was used to perform a post-hoc adjustment on the standard errors to account for the nesting of individuals within cohorts.

Prenatal substance use classes were then used to predict levels of child behavior in two latent class–adjusted regression models, one for each behavior category of interest (ie, externalizing and internalizing behavior scores). Child (ethnicity/race, child sex, child age) and maternal characteristics (education, maternal age at delivery, and marital status) were included concurrently as predictors of CBCL behavior outcome in each model. Gestational age, while statistically different between classes, only differed by approximately 3 days, and therefore was not adjusted within the model. Sample size considerations required ethnicity/race to be classified into one of three mutually exclusive categories: non-Hispanic/White, non-Hispanic/non-White (ie, Black, Asian, Alaska Native, American Indian, native Hawaiian, and Pacific Islander), or Hispanic. See Supplementary Materials for more information. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the associations between predictors and the categorical variable of prenatal substance use class membership for each of the CBCL outcome models. Beta estimates were listed for continuous associations. The Wald chi-squared test was used to analyze group differences between latent class means to determine if mean behavior scores were different between the latent classes. Pairwise comparisons between the three latent classes were also conducted within the model with z-tests, accounting for covariates and measurement error. Cohen's d was calculated for each statistically significant pairwise comparison. Analyses[30,31] were performed in Mplus 8.16.[36]

RESULTS

Latent Classes of Prenatal Substance Use

A three-class solution fit the data well based on Bayesian Information Criterion values and the Lo-Mendell-Rubin likelihood ratio test (p=.045; Table 3; online). Average posterior class probabilities ranged from 0.52 to 0.99. We described the classes as an illicit substance use class (n=64; 2.9%) with the highest use of opioids (23%) and illicit substances (100%); a licit substance use class (n=145; 6.6%) characterized by nicotine (95%), alcohol (68%), and marijuana use (48%); and a low substance use class (n=1,986; 90.5%) with either no or minimal alcohol (10%) and nicotine use (9%) identified during pregnancy (average number of substances used: M=.2, SD=.4). All the illicit substance use in our sample was identified within the illicit substance class, including use of cocaine, methamphetamine, and heroin; women in this class also used nicotine, alcohol, marijuana, and prescription opioids. The licit substance use class had the highest percentage of nicotine and alcohol use. Women in the illicit and the licit substance use classes had comparable levels of marijuana (55% and 48%, respectively) and prescription opioid use (17% and 14%, respectively). Women in these two substance use classes used more than two substances on average (M=2.9, SD=.8; M=2.2, SD=.5, respectively), indicating polysubstance use. These latent classes also statistically differed by maternal age, maternal ethnicity/race, education, and depression diagnosis (p<.05); for full demographic results see Table 2 and Supplementary Materials.

Prenatal Substance Use Classes and CBCL Scores

Prenatal substance use class membership predicted externalizing behavior scores (Wald (2)=83.08, p<.001) and internalizing behavior scores (Wald (2)=34.58, p<.001; Table 4). Children born to women in the licit use class had higher levels of externalizing behavior (M=54.6, SD=11.1) than children of women in the low use class (M=47.7, SD=10.5; b=5.52, p=.001, d=0.64). Children born to women in the illicit use class had higher, yet not statistically significant levels of externalizing behavior (M=51.1, SD=11.2) than women in the low use class (b=3.05, p=.073). Externalizing behavior was not statistically different between the illicit and licit use classes (b=−2.46, p=.45).

Children born to women in the illicit use class had slightly higher levels of internalizing behavior (M=50.3, SD=10.9) than children of women in the low use class (M=48.5, SD=10.7, b=1.72, p<.001, d=0.16). Although the mean for internalizing behavior in the licit use class (M=52.1, SD=10.8) was higher than the illicit use class, when accounting for sample size, covariates, and measurement error within the model, no statistically significant differences in internalizing behavior were found in the licit and low use classes (b=2.93, p=.14). Internalizing behavior was not statistically different between the illicit and licit use classes (b=−1.21, p=.50).

Predictors of Prenatal Substance Use Class Membership and CBCL Scores

For both behavioral outcomes, maternal education, ethnicity/race, and marital status significantly predicted substance use class membership. Mothers with a high school diploma or greater were less likely to be in the illicit use class than the licit use class for externalizing (OR=.27, 95% CI[.13,.56]) and internalizing models (OR=.27, 95% CI[.12,.57]). Married mothers (externalizing: OR=.04, 95% CI[.02,.12]; internalizing: OR=.04, 95% CI[.01,.14]), respectively) were more likely to be in the low use class than the licit use class compared with unmarried mothers, and non-Hispanic/White mothers (externalizing: OR=17.66, 95% CI[3.02,103.37]; internalizing: OR=19.56, 95% CI[2.31,165.36]) were more likely to be in the licit use class than the low use class compared with non-Hispanic/non-White mothers. Maternal age at delivery did not predict class membership for either problem behavior (Table 5).

Child sex, child ethnicity/race, and maternal marital status significantly predicted externalizing behavior. Higher externalizing scores were more likely in male children (b=1.31, 95% CI[.94,1.68]), non-Hispanic/White (b=1.37, 95% CI[.53,2.21]) and Hispanic children (b=1.67, 95% CI[.43,2.92]), and children with an unmarried mother (b=−2.23, 95% CI[−3.56,−.89]) than female children, non-Hispanic/non-White children, and children with married mothers. Child sex and ethnicity/race significantly predicted internalizing behavior scores. Higher internalizing scores were more likely in male children (b=1.78, 95% CI[1.13,2.45]) and non-Hispanic/White (b=1.43, 95% CI[.49,2.37]) children than female children and non-Hispanic/non-White children. Child age at CBCL administration, maternal education, and maternal age at delivery did not predict problem behaviors (Table 6).

DISCUSSION

Polysubstance use may have unique impacts on children's behavior problems. We harmonized prenatal characteristics and behavioral outcomes for a dataset comprising children born to women (N=2,195) from 10 ECHO-wide cohorts who were asked about substance use during pregnancy. We identified three unique classes of women based on their prenatal substance use profiles and examined the influence of these substance use classes and sociodemographic characteristics on behavioral problems at ages 6–11 years.

Mothers in the largest and most normative substance use class (90.5%; n=1,986) had little to no substance use during their pregnancy. The remaining two classes accounted for most of the substance use in our study sample. However, the substance use between these two classes were unique, with one class comprised mainly of illicit substance use (2.9%; n=64)—women who primarily used illicit drugs, along with licit substances (e.g., nicotine, alcohol, marijuana, and prescription opioids)—and the other class made up of licit substance use only (6.6%; n=145)—women who used nicotine, alcohol, marijuana, and prescription opioids, with no reported illicit substance use. The average number of substances used in the illicit and licit use classes was above two, emphasizing the prevalence of polysubstance use compared with single substance use during pregnancy.[37,38] Further, the distinction of these classes underlines the differences in polysubstance use profiles, which may help shed light on how types of substances predict specific child behavioral outcomes.

Children born to women in the licit use class—characterized by a higher likelihood of using nicotine and alcohol than the illicit and low substance use classes—showed statistically significant elevations in externalizing behavior than children who had low to no in utero substance exposure. These results are consistent with single substance exposure studies on alcohol and nicotine use and child externalizing behavior problems.[39,40] However, the average externalizing behavior score for this licit substance use class was in the typical range (i.e., several children had subclinical externalizing scores). Nevertheless, around 1 in 4 of children in this class had borderline/clinical levels of externalizing behavior, suggesting that children prenatally exposed to nicotine and alcohol, compared with other types of substance exposures, are at higher risk of developing externalizing behavior problems in middle childhood.

In contrast, children born to women belonging to the illicit use class—characterized by a higher likelihood of using cocaine, methamphetamine, and heroin, along with nicotine, alcohol, marijuana, and prescription opioids—showed very small but statistically significant elevations in internalizing behavior problems than children who had low to no in utero substance exposure. Our findings are consistent with one previous study on polysubstance exposure in middle childhood, and the few individual substance exposure (eg, opioids, marijuana) studies that found prenatal substance use predicted child internalizing behavior problems.[16–18] Yet, the average internalizing behavior score for this class remained below the clinical range, indicating some children had subclinical scores. To our knowledge, this is the first large-scale, multi-cohort study showing in utero polysubstance exposure to primarily illicit substances predicts internalizing behavior problems in middle childhood. More research is needed to examine potential prenatal mechanisms associated with these different child behaviors outcomes based on type and/or combination of in utero substance exposures.

Maternal and child factors were associated with class membership and CBCL scores. Non-Hispanic/White mothers and married mothers were more likely to use low or no substances than licit substances, and married mothers were less likely to use illicit than licit substances, suggesting that mothers with lower education and those who identify as a racial minority may be a higher risk for substance use. Moreover, male children and non-Hispanic/White children were more likely to have high externalizing and internalizing scores; Hispanic children and children with unmarried mothers were also more likely to have elevated externalizing behavior. These findings highlight potential identifiers of risk for childhood behavioral problems and may help inform targeted interventions.

This study has several limitations. Due to the design of the study, we did not account for the postnatal caregiving environment, which can impact child behavioral outcomes. Additionally, we classified prescription opioids as licit, although we recognize they can be obtained illegally. Further, as each cohort was not necessarily designed to study prenatal substance use, we were reliant primarily on maternal self-report. Women may feel uncomfortable reporting their substance use[41] and may have difficulty recalling past substance use;[42] therefore, self-report measures can be biased and use is likely underreported.

Reliance on maternal reports of child behavior rather than clinical diagnostic assessments also limits our ability to draw firm conclusions, despite the established validity of the CBCL. Finally, with only 39% completed data, we were unable to account for maternal depression. Maternal mental health or other direct genetic influences may partially explain the link between prenatal substance use and child behavior problems. Future studies should use repeated measurements of the CBCL and/or other child behavior measures to enhance the ability to draw conclusions from the data. They should also assess child behavior in adolescence, including ratings of attention and hyperactivity, when internalizing behaviors may be more apparent to parents and adolescents can self-report their own behavior.

In summary, our findings document the varied types and prevalence of substance use during pregnancy, which was present even among women in our low substance use class. Furthermore, the distribution of women into three substance use classes underscores the variations in polysubstance use profiles. Children exposed to nicotine and alcohol in utero showed higher rates of externalizing behavior, and children exposed to illicit substances had higher rates of internalizing behavior than children with little to no exposures. Although the type of child behavior problem was differentiated based on the unique substance use profiles, both licit and illicit polysubstance exposures during gestation appear detrimental to child behavioral outcomes, with around 1 in 5 children having borderline or clinical levels of behavioral problems. Reducing illicit substance use with medication-assisted treatment programs, eliminating co-substance use that adversely alters pharmacodynamics, and moderating legal substance use in birthing parents may limit the risk for childhood behavioral problems. Further, it is vital to screen for behavioral risk early in development when interventions are more successful.

While children with polysubstance exposure showed more problem behaviors than children with less or no exposure, the variability of scores suggests that some children may be more resilient than others. Examining household and child characteristics in these between-child differences may offer insight into resiliency factors and help identify children at higher risk for developmental disruptions. Similar large-scale prenatal substance exposure studies may help bridge smaller mechanistic studies of the impact of in utero substance exposure on child outcomes. Overall, these findings highlight the need for further large-scale studies across diverse geographic locations that include both clinical and general populations, like the HEALthy Brain and Child Development Study,[43] to identify children's risk for developmental disruptions based on maternal prenatal substance use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

The de-identified datasets for this manuscript are publicly available on Data and Specimen Hub (DASH). https://dash.nichd.nih.gov/study/417122

Abbreviations:

CBCL	Child Behavior Checklist
ECHO	Environmental influences on Child Health Outcomes
FASD	fetal alcohol spectrum disorder
FCS	fully conditional specification

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Table 1.

Participant Demographic Information by Cohort

Characteristics	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	Cohort 7	Cohort 8	Cohort 9	Cohort 10	Overall
Sample size, N(%)	**127(5.8%)**	**130(5.9%)**	**925(42.1%)**	**114(5.2%)**	**478(21.8%)**	**<5**	**<10**	**77(3.5%)**	**165(7.5%)**	**171(7.8%)**	**2195(100%)**
Maternal demographics											
Age at delivery, *N*(%)	**126(99.2%)**	**130(100%)**	**925(100%)**	**114(100%)**	**478(100%)**	**<5**	**<10(100%)**	**77(100%)**	**165(100%)**	**171(100%)**	**2194(100%)**
Mean(SD)	29.9(6.5)	30.6(5.8)	27.3(5.6)	32(5.5)	24.5(5.9)	36	34.6(4.2)	29.6(4.6)	31(5.4)	31.6(5.3)	28(6.2)
Ethnicity/Race,*N*(%)	**123(96.9%)**	**125(96.2%)**	**925(100%)**	**114(100%)**	**478(100%)**	**<5**	**<10(100%)**	**75(97.4%)**	**165(100%)**	**171(100%)**	**2184(99.5%)**
Non-Hispanic White	89(72%)	78(62%)	304(33%)	85(75%)	345(72%)	<5	6(86%)	73(97%)	61(37%)	127(74%)	1169(54%)
Non-Hispanic Black	<5	8(6%)	557(60%)	<5	65(14%)	0(0%)	0(0%)	<5	24(15%)	15(9%)	674(31%)
Non-Hispanic Asian	<5	8(6%)	7(1%)	<5	10(2%)	0(0%)	0(0%)	0(0%)	10(6%)	9(5%)	47(2%)
Non-Hispanic Other	10(8%)	8(6%)	41(4%)	10(9%)	30(6%)	0(0%)	0(0%)	0(0%)	12(7%)	10(6%)	121(6%)
Hispanic	21(17%)	23(18%)	16(2%)	15(13%)	28(6%)	0(0%)	<5	<5	58(35%)	10(6%)	173(8%)
Education, *N*(%)	**124(97.6%)**	**128(98.5%)**	**925(100%)**	**114(100%)**	**473(99%)**	**<5**	**<10(100%)**	**77(100%)**	**165(100%)**	**171(100%)**	**2185(99.5%)**
< High school	<5	<5	96(10%)	<5	88(19%)	0(0%)	0(0%)	0(0%)	28(17%)	13(8%)	231(11%)
High school	<10	<10	422(46%)	<15	175(37%)	0(0%)	0(0%)	0(0%)	11(7%)	10(6%)	645(30%)
Some college and above	114(92%)	121(95%)	407(44%)	98(86%)	210(44%)	<5	<10(100%)	77(100%)	126(76%)	148(87%)	1309(60%)
Marital status, *N*(%)	**0(0%)**	**0(0%)**	**924(99.9%)**	**108(94.7%)**	**8(1.7%)**	**0(0%)**	**0(0%)**	**38(49.4%)**	**141(85.5%)**	**171(100%)**	**1390(63.3%)**
Married or living with a partner			547(59%)	90(83%)	0(0%)			36(95%)	113(80%)	151(88%)	937(67%)
Insurance type, *N*(%)	**0(0%)**	**0(0%)**	**925(100%)**	**114(100%)**	**0(0%)**	**0(0%)**	**0(0%)**	**0(0%)**	**18(10.9%)**	**0(0%)**	**1057(48.2%)**
Any insurance			924(100%)	110(96%)					18(100%)		1052(100%)
Medicare/Medicaid			528(57%)	29(26%)					12(67%)		569(54%)
Private			413(45%)	86(78%)					6(33%)		505(93%)
Other			<15	<5					6(35%)		17(2%)
No Insurance			<5	<5					0(0%)		5(<1%)
Substance use data											
Collection method *N*(%)											
Self-Report											

Characteristics	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	Cohort 7	Cohort 8	Cohort 9	Cohort 10	Overall
Sample size, N(%)	**127(5.8%)**	**130(5.9%)**	**925(42.1%)**	**114(5.2%)**	**478(21.8%)**	**<5**	**<10**	**77(3.5%)**	**165(7.5%)**	**171(7.8%)**	**2195(100%)**
Maternal demographics											
Opioid	127(100%)	129(99%)	925(100%)	114(100%)	478(100%)	<5(100%)	<10(100%)	77(100%)	165(100%)	171(100%)	2194(100%)
Alcohol	122(100%)	75(100%)	925(100%)	112(100%)	476(100%)	<5(100%)	<5(100%)	77(100%)	165(100%)	171(100%)	2125(100%)
Nicotine	94(100%)	125(100%)	925(100%)	114(100%)	477(100%)	<5(100%)	<5(100%)	77(100%)	165(100%)	171(100%)	2150(100%)
Marijuana	100(100%)	124(100%)	925(100%)	114(100%)	475(100%)	<5(100%)	<5(100%)	77(100%)	165(100%)	171(100%)	2153(100%)
Illicit Drugs	126(100%)	116(100%)	925(100%)	109(100%)	477(100%)	<5(100%)	<5(100%)	77(100%)	165(100%)	170(100%)	2167(100%)
Medical Record											
Opioid	0(0%)	40(31%)	0(0%)	0(0%)	384(80%)	0(0%)	0(0%)	0(0%)	162(98%)	0(0%)	586(27%)
Alcohol	0(0%)	9(12%)	0(0%)	0(0%)	433(91%)	0(0%)	0(0%)	0(0%)	165(100%)	0(0%)	607(29%)
Nicotine	0(0%)	9(7%)	0(0%)	0(0%)	434(91%)	0(0%)	0(0%)	0(0%)	165(100%)	0(0%)	608(28%)
Marijuana	0(0%)	8(6%)	0(0%)	0(0%)	433(91%)	0(0%)	0(0%)	0(0%)	165(100%)	0(0%)	606(28%)
Illicit Drugs	0(0%)	7(6%)	0(0%)	0(0%)	435(91%)	0(0%)	0(0%)	0(0%)	165(100%)	0(0%)	607(28%)
Child characteristics											
Sex, *N*(%)	**127(100%)**	**130(100%)**	**925(100%)**	**114(100%)**	**478(100%)**	**<5**	**<10(100%)**	**77(100%)**	**165(100%)**	**171(100%)**	**2195(100%)**
Male	73(57%)	98(75%)	457(49%)	60(53%)	267(56%)	<5	<5	44(57%)	94(57%)	88(51%)	1186(54%)
Female	54(43%)	32(25%)	468(51%)	54(47%)	211(44%)	0(0%)	<5	33(43%)	71(43%)	83(49%)	1009(46%)
Child race/ethnicity, *N*(%)	**124(97.6%)**	**130(100%)**	**924(99.9%)**	**114(100%)**	**478(100%)**	**<5**	**<10(100%)**	**77(100%)**	**165(100%)**	**171(100%)**	**2191(99.8%)**
Non-Hispanic White	82(66%)	68(52%)	275(30%)	76(67%)	261(55%)	<5	<10(86%)	74(96%)	58(35%)	111(65%)	1012(46%)
Non-Hispanic Black	<5	8(6%)	573(62%)	<5	63(13%)	0(0%)	0(0%)	0(0%)	25(15%)	18(11%)	691(32%)
Non-Hispanic Asian	0(0%)	5(4%)	6(1%)	<5	<5	0(0%)	0(0%)	0(0%)	5(3%)	11(6%)	29(1%)
Non-Hispanic Other	16(13%)	18(14%)	38(4%)	<15(12%)	89(19%)	0(0%)	0(0%)	<5	16(10%)	16(9%)	208(9%)
Hispanic	24(19%)	31(24%)	32(3%)	21(18%)	64(13%)	0(0%)	<5	<5	61(37%)	15(9%)	251(11%)
Gestational age at birth, *N*(%)	**125(98.4%)**	**130(100%)**	**925(100%)**	**114(100%)**	**350(73.2%)**	**<5**	**<10(100%)**	**76(98.7%)**	**165(100%)**	**171(100%)**	**2064(94%)**
Mean(SD)	38.9(1.5)	38.6(2.3)	38.7(1.8)	37.2(3.9)	38.9(1.9)	36	39.9(1.5)	38.7(1.8)	38.8(1.7)	39.2(2.1)	38.7(2.1)
Birth weight (kg), *N*(%)	**124(97.6%)**	**128(98.5%)**	**920(99.5%)**	**106(93%)**	**465(97.3%)**	**<5**	**<10(100%)**	**68(88.3%)**	**165(100%)**	**170(99.4%)**	**2154(98.1%)**
Mean(SD)	3.4(0.5)	3.4(0.7)	3.3(0.6)	3.1(1)	3.3(0.5)	2.9	3.7(0.8)	3.4(0.5)	3.3(0.5)	3.4(0.5)	3.3(0.6)
Size for gestational age at birth, *N*(%)	**21(17%)**	**31(24%)**	**113(12%)**	**25(24%)**	**43(13%)**	**0(0%)**	**<5**	**<15(21%)**	**26(16%)**	**28(16%)**	**304(15%)**

Characteristics	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	Cohort 7	Cohort 8	Cohort 9	Cohort 10	Overall
Sample size, N(%)	**127(5.8%)**	**130(5.9%)**	**925(42.1%)**	**114(5.2%)**	**478(21.8%)**	**<5**	**<10**	**77(3.5%)**	**165(7.5%)**	**171(7.8%)**	**2195(100%)**
Maternal demographics											
Large	21(17%)	31(24%)	113(12%)	25(24%)	43(13%)	0(0%)	<5	<15(21%)	26(16%)	28(16%)	304(15%)
Small	9(7%)	8(6%)	77(8%)	6(6%)	28(8%)	0(0%)	<5	<5	13(8%)	11(6%)	154(8%)
Child age (years) at CBCL, *N*(%)	**127(100%)**	**130(100%)**	**925(100%)**	**114(100%)**	**478(100%)**	**<5**	**<10(100%)**	**77(100%)**	**165(100%)**	**171(100%)**	**2195(100%)**
Mean(SD)	**8.5(1.7)**	**9.5(1.1)**	**9.6(1.3)**	**7.3(0.9)**	**9.2(1.8)**	**6**	**10(1.5)**	**9(0)**	**7.7(0.9)**	**7.3(1)**	**9(1.6)**

Note. Means and standard deviations are presented for continuous variables while the number of observations and percent of total observations are presented for categorical variables. Substance use data collection methods were reported for the available data reports per cohort (ie, excluding any missing data in the percentage calculations). Most substance use data was collected via self-report.

CBCL, Child Behavior Checklist; SD, standard deviation.

Table 2.

Sample Characteristics by Prenatal Drug Exposure Classes and Overall

Characteristics	Class 1 (Illicit substance use)	Class 2 (Licit substance use)	Class 3 (Low substance use)	Overall	Missing data	*p*-value
Sample size	**64(2.9%)**	**145(6.6%)**	**1986(90.5%)**	**2195(100%)**		
Maternal demographics						
Age at delivery, *N*(%)	**64(100%)**	**145(100%)**	**1985(99.9%)**	**2194(100%)**	1(<1%)#	
Mean (SD)	28(6.7)	25(5.9)	28(6.1)	28(6.2)		<0.001
Ethnicity/Race, *N*(%)	**64(100%)**	**145(100%)**	**1975(99.4%)**	**2184(99.5%)**	11(<1%)#	
Non-Hispanic/White	38(59%)	117(81%)	1014(51%)	1169(54%)		<0.001
Non-Hispanic/Black	19(30%)	7(5%)	648(33%)	674(31%)		<0.001
Non-Hispanic/Asian	0(0%)	2(1%)	45(2%)	47(2%)		0.374
Non-Hispanic/Other	4(6%)	12(8%)	105(5%)	121(6%)		0.313
Hispanic	3(5%)	7(5%)	163(8%)	173(8%)		0.21
Calendar year of child birth, *N*(%)	**64(100%)**	**145(100%)**	**1986(100%)**	**2195(100%)**	0	
2001–2010	58(91%)	119(82%)	1176(59%)	1353(62%)		<0.001
2011–2020	6(9%)	26(18%)	810(41%)	842(38%)		<0.001
Socioeconomic status						
Education, *N*(%)	**64(100%)**	**143(98.6%)**	**1978(99.6%)**	**2185(99.5%)**	10(<1%)#	
< High school	12(19%)	30(21%)	189(10%)	231(11%)		<0.001
High school	26(41%)	48(34%)	571(29%)	645(30%)		0.07
Some college and above	26(41%)	65(45%)	1218(62%)	1309(60%)		<0.001
Marital status, *N*(%)	**20(31.3%)**	**31(21.4%)**	**1339(67.4%)**	**1390(63.3%)**	805(36.7%)#	
Married or living with a partner	12(60%)	18(58%)	907(68%)	937(67%)		0.407
Insurance type, *N*(%)	**20(31.3%)**	**17(11.7%)**	**1020(51.4%)**	**1057(48.2%)**	1,175(53.5%)	
Any insurance	20(100%)	17(100%)	1015(100%)	1052(100%)		0.913
Medicare/Medicaid	19(95%)	8(47%)	542(53%)	569(54%)		0.001
Private	1(100%)	9(82%)	495(94%)	505(93%)		0.291
Other	0(0%)	0(0%)	17(2%)	17(2%)		0.745

Characteristics	Class 1 (Illicit substance use)	Class 2 (Licit substance use)	Class 3 (Low substance use)	Overall	Missing data	*p*-value
Sample size	**64(2.9%)**	**145(6.6%)**	**1986(90.5%)**	**2195(100%)**		
Maternal demographics						
No Insurance	0(0%)	0(0%)	5(<1%)	5(<1%)		0.913
Comorbidities						
History of depression through 8 weeks postpartum, *N*(%)	**37(57.8%)**	**106(73.1%)**	**714(36%)**	**857(39%)**	1338(61.0%)	
Yes	14(38%)	31(29%)	132(18%)	177(21%)		0.001
Depression during pregnancy, *N*(%)	**37(57.8%)**	**101(69.7%)**	**560(28.2%)**	**698(31.8%)**	1497(68.2%)	
Yes	14(38%)	29(29%)	90(16%)	133(19%)		<0.001
Substance use during pregnancy						
Alcohol, *N*(%)	**64(100%)**	**144(99.3%)**	**1917(96.5%)**	**2125(96.8%)**	70(3.2%)[#]	
Yes	24(38%)	98(68%)	195(10%)	317(15%)		<0.001
Nicotine, *N*(%)	**64(100%)**	**143(98.6%)**	**1943(97.8%)**	**2150(97.9%)**	45(2.1%)[#]	
Yes	48(75%)	136(95%)	181(9%)	365(17%)		<0.001
Marijuana, *N*(%)	**64(100%)**	**145(100%)**	**1945(97.9%)**	**2154(98.1%)**	41(1.9%)[#]	
Yes	35(55%)	70(48%)	21(1%)	126(6%)		<0.001
Any Illicit Drugs[*], *N*(%)	**64(100%)**	**144(99.3%)**	**1960(98.7%)**	**2168(98.8%)**	27(1.2%)[#]	
Yes	64(100%)	0(0%)	0(0%)	64(3%)		<0.001
Methamphetamine, *N*(%)	**56(87.5%)**	**124(85.5%)**	**1830(92.1%)**	**2010(91.6%)**	185(8.4%)[#]	
Yes	16(29%)	0(0%)	0(0%)	16(1%)		<0.001
Cocaine, *N*(%)	**62(96.9%)**	**144(99.3%)**	**1964(98.9%)**	**2170(98.9%)**	25(1.1%)[#]	
Yes	25(40%)	0(0%)	0(0%)	25(1%)		<0.001
Opioid use						
Use during pregnancy, *N*(%)	**64(100%)**	**145(100%)**	**1986(100%)**	**2195(100%)**	0	
Yes	15(23%)	20(14%)	20(1%)	55(3%)		<0.001
Prescription use, *N*(%)	**42(65.6%)**	**123(84.8%)**	**728(36.7%)**	**893(40.7%)**	1299(59.3%)	
Yes	7(17%)	20(16%)	20(3%)	47(5%)		<0.001
Heroin, *N*(%)	**64(100%)**	**139(95.9%)**	**1857(93.5%)**	**2060(93.8%)**	135(6.2%)	

Characteristics	Class 1 (Illicit substance use)	Class 2 (Licit substance use)	Class 3 (Low substance use)	Overall	Missing data	*p*-value
Sample size	**64(2.9%)**	**145(6.6%)**	**1986(90.5%)**	**2195(100%)**		
Maternal demographics						
Yes	10(16%)	0(0%)	0(0%)	10(<1%)		<0.001
Total number of substance use, *N*(%)	**64(100%)**	**142(97.9%)**	**1875(94.4%)**	**2081(94.8%)**	114(5.2%)	
Mean (SD)	2.9(0.8)	2.2(0.5)	0.2(0.4)	0.4(0.8)		<0.001
Any substance use	64(100%)	142(100%)	402(21%)	608(29%)		<0.001
Child characteristics						
Sex, *N*(%) with data	**64(100%)**	**145(100%)**	**1986(100%)**	**2195(100%)**	0	
Male	38(59%)	74(51%)	1074(54%)	1186(54%)		0.532
Female	26(41%)	71(49%)	912(46%)	1009(46%)		
Child ethnicity/race, *N*(%)	**64(100%)**	**145(100%)**	**1982(99.8%)**	**2191(99.8%)**	4(<1%)[#]	
Non-Hispanic/White	29(45%)	95(66%)	888(45%)	1012(46%)		<0.001
Non-Hispanic/Black	21(33%)	5(3%)	665(34%)	691(32%)		<0.001
Non-Hispanic/Asian	0(0%)	0(0%)	29(1%)	29(1%)		0.212
Non-Hispanic/Other	5(8%)	29(20%)	174(9%)	208(9%)		<0.001
Hispanic	9(14%)	16(11%)	226(11%)	251(11%)		0.795
Gestational age at birth, *N*(%)	**55(85.9%)**	**127(87.6%)**	**1882(94.8%)**	**2064(94%)**	131(4.6%)	
Mean(SD)	38.4(2.5)	39.2(1.7)	38.7(2.1)	38.7(2.1)		0.017
Birth weight (kg), *N*(%)	**63(98.4%)**	**142(97.9%)**	**1949(98.1%)**	**2154(98.1%)**	41(1.9%)	
Mean(SD)	3.1(0.6)	3.3(0.5)	3.3(0.6)	3.3(0.6)		0.109
Size for gestational age at birth, *N*(%)	**54(84.4%)**	**124(85.5%)**	**1843(92.8%)**	**2021(92.1%)**	174(7.9%)	
Large for gestational age	7(13%)	13(10%)	284(15%)	304(15%)		0.302
Small for gestational age	7(13%)	6(5%)	141(8%)	154(8%)		0.169
Child age (years) at CBCL-Sch assessment, *N*(%)	**64(100%)**	**145(100%)**	**1986(100%)**	**2195 (100%)**	0	
Mean(SD)	9.3(1.6)	9.1(1.8)	9(1.6)	9(1.6)		0.259

Note. Means and standard deviations are presented for continuous variables while the number of observations and percent of total observations are presented for categorical variables.

[*] Includes any recreational, illicit or street drugs, such as cocaine, heroin, methamphetamine (Meth), MDMA (ecstasy), speed (amphetamine sulfate), acid/LSD, Special K (ketamine), and others.

[#] Denotes missing data that was imputed with multiple imputation.

CBCL, Child Behavior Checklist; SD, standard deviation.

Table 3.

Model Fit Statistics

Class	Log likelihood	# of free parameters	BIC	ssaBIC	Entropy	LMR	LMT *p*-value	BLRT	BLRT *p*-value	Smallest class
1 class	−2900.073	5	5838.615	5822.73						
2 class	−2643.154	11	5370.941	5335.993	0.815	502.943	<.001	−2900.073	<.001	9.60%
3 class	**−2635.785**	**17**	**5402.367**	**5348.355**	**0.844**	**14.426**	**0.045**	**−2643.154**	**0.0625**	**2.90%**
4 class	−2631.479	23	5439.919	5366.845	0.888	8.428	0.1178	−2635.785	0.2857	1.70%

Note. Lower values of BIC and ssaBIC indicate better model fit. Entropy above .80 indicates that there is good classification of individuals. For LMT and BLRT, a p-value $\leq$.05 suggests that the subsequent model provides a statistically significant improvement in model fit. The final three-class solution accepted in bold. BIC, Bayesian Information Criterion; ssaBIC, Bayesian Information Criterion in subject level; LMR, Lo-Mendell-Rubin likelihood ratio test; BLRT, Bootstrap Likelihood Ratio Test.

Table 4.

Model Predicted CBCL T-scores by Prenatal Substance Use Latent Classes and Children in the Borderline or Clinical Range

Outcomes	Prenatal substance use latent classes				
	Full sample	**Illicit use (2.9%) [Class 1]**	**Licit use (6.6%) [Class 2]**	**Low use (90.5%) [Class 3]**	**Pairwise comparisons**
CBCL-Sch – Externalizing T-Score, Mean (SD)*	49 (10.6)	51.1(11.2)	54.6(11.1)	47.7(10.5)	1 v. 2, $p = .45$ 1 v. 3, $p = .07$ 2 > 3, $p = .001$, $d = 0.64$
Borderline or clinical range, N (%)	350 (16%)	15(23%)	41(28%)	294(15%)	
CBCL-Sch – Internalizing T-Score, Mean (SD)*	49 (10.8)	50.3(10.9)	52.1(10.8)	48.5(10.7)	1 v. 2, $p = .50$ 1 > 3, $p < .001$, $d = 0.16$ 2 v. 3, $p = .14$
Borderline or clinical range, N (%)	405(18%)	13(20%)	36(25%)	356(18%)	

Note. Class 3: Low Substance Use serves as the referent. Scores greater than 60 represent scores in the borderline or clinical range.

* Denotes significant ($p < .05$) omnibus Wald chi-squared test of group difference between latent class means CBCL-Sch, Child Behavior Checklist-School aged version.

Table 5.

Predictors of Latent Class Membership for Each CBCL Outcome Model

	CBCL externalizing behavior t-score model	
Covariates	**Illicit use vs. licit use**	**Licit class vs. low use**
	OR (95% CI)	OR (95% CI)
Maternal education (above high school)	**0.27 (0.13, 0.56)**	0.77 (0.50, 1.18)
Maternal ethnicity/race		
Non-Hispanic/non-White	1.00 ref	1.00 ref
Non-Hispanic/White	2.66 (0.85, 8.32)	**17.66 (3.02, 103.37)**
Hispanic	0.84 (0.19, 3.68)	2.46 (0.35, 17.16)
Marital status (married/partnered vs. not)	0.66 (0.13, 3.32)	**0.04 (0.02, 0.12)**
Maternal age at delivery, Years	1.04 (0.94, 1.15)	0.98 (0.96, 1.01)
	CBCL internalizing behavior t-score model	
Covariates	Illicit use vs. licit use	Licit class vs. low use
	OR (95% CI)	OR (95% CI)
Maternal education (above high school)	**0.27 (0.12, 0.57)**	0.75 (0.39, 1.45)
Maternal ethnicity/race		
Non-Hispanic/non-White	1.00 ref	1.00 ref
Non-Hispanic/White	2.66 (0.84, 8.40)	**19.56 (2.31, 165.36)**
Hispanic	0.84 (0.19, 3.67)	2.56 (0.28, 23.50)
Marital status (married/partnered vs. not)	0.66 (0.13, 3.28)	**0.04 (0.01, 0.14)**
Maternal age at delivery, years	1.04 (0.94, 1.15)	0.98 (0.95, 1.01)

Note. Results are presented for both outcome behaviors of interest: externalizing behavior (model 1) and internalizing behavior scores (model 2). Odds ratios (OR) were calculated for interpretability. Bolded results were significant at $p < .05$.

CBCL, Child Behavior Checklist.

Table 6.

Predictors of CBCL T-scores

	CBCL externalizing behavior t-score	CBCL internalizing behavior t-score
	***b* (95%CI)**	***b* (95%CI)**
CBCL-Sch age at administration	−0.50 (−0.93, −0.07)	0.04 (−0.52, 0.60)
Child male sex	**1.31 (0.94, 1.68)**	**1.78 (1.13, 2.45)**
Maternal education (above high school)	−0.21 (−1.28, 0.85)	0.99 (−0.20, 2.17)
Child ethnicity/race		
Non-Hispanic/non-White	ref	ref
Non-Hispanic/White	**1.37 (0.53, 2.21)**	**1.43 (0.49, 2.37)**
Hispanic	**1.67 (0.43, 2.92)**	1.87 (−0.23, 3.96)
Maternal age at delivery, years	−0.01 (−0.06, 0.04)	0.01 (−0.08, 0.09)
Maternal marital status (married/partnered vs. not)	**−2.23 (−3.56, −0.89)**	−1.13 (−2.35, 0.08)

Note. Bolded results were significant at p < .05.

CBCL, Child Behavior Checklist; CBCL-Sch, Child Behavior Checklist-School-aged version; CI, confidence interval.