Latent Class Analysis of Prenatal Substance Exposure and Child Behavioral Outcomes

Sarah E. Maylott, PhD[1,2], Elisabeth Conradt, PhD[1,2], Monica McGrath, ScD[3], Emily A. Knapp, PhD[3], Xiuhong Li, MAS[3], Rashelle Musci, PhD[4], Judy Aschner, MD[5,6], Lyndsay A. Avalos, PhD[7], Lisa A. Croen, PhD[7], Sean Deoni, PhD[8], Karen Derefinko, PhD[9], Amy Elliott, PhD[10], Julie A. Hofheimer, PhD[11], Leslie D. Leve, PhD[12], Juliette C. Madan, MS, MD[13], Maxwell Mansolf, PhD[14], Liza B. Murrison, PhD, MPH[15,16], Jenae M. Neiderhiser, PhD[17], Sally Ozonoff, PhD[18], Jonathan Posner, MD[1], Amy Salisbury, PhD[19], Sheela Sathyanarayana, MD, MPH[20,21], Julie B. Schweitzer, PhD[22], Carl Seashore, MD[11], Meagan E. Stabler, PhD[23], Leslie W. Young, MD[24], Steven J. Ondersma, PhD[25], and Barry Lester, PhD[26], on behalf of program collaborators for Environmental influences on Child Health Outcomes (ECHO)*

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 Program, we harmonized prenatal substance use data and child behavior outcomes from 2195 women and their 6- to 11-year-old children across 10 cohorts in the US 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 = 1986), 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 greater 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 multicohort, large-scale studies to examine childhood outcomes based on prenatal substance use profiles. *(J Pediatr 2023;260:113468)*.

Prenatal substance use continues to be a major public health issue. In the US, 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 1 substance in isolation is infrequent, with upwards of 50% of pregnant women using 1 substance and reporting use of at least 1 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 greater 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

CBCL	Child Behavior Checklist
ECHO	Environmental influences on Child Health Outcomes

From the [1]Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC; [2]Department of Psychology, University of Utah, Salt Lake City, UT; [3]Department of Epidemiology, and [4]Department of Mental Health, Johns Hopkins School of Public Health, Baltimore, MD; [5]Department of Pediatrics, Hackensack Meridian School of Medicine, Nutley, NJ; [6]Albert Einstein College of Medicine, Bronx, NY; [7]Division of Research, Kaiser Permanente Northern California, Oakland, CA; [8]Department of Pediatrics and Department of Diagnostic Imaging, Alpert Medical School of Brown University, Providence, RI; [9]Department of Preventive Medicine and Department of Pharmacology, Addiction Science, and Toxicology, The University of Tennessee Health Science Center, Memphis, TN; [10]Avera Research Institute and Department of Pediatrics, University of South Dakota School of Medicine, Sioux Falls, SD; [11]Department of Pediatrics, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC; [12]Prevention Science Institute, University of Oregon, Eugene, OR; [13]Department of Pediatrics, Psychiatry and Epidemiology, Geisel School of Medicine at Dartmouth, Hanover, NH; [14]Department of Medical Social Sciences, Feinberg School of Medicine, Northwestern University, Chicago, IL; [15]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH; [16]Division of Asthma Research, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [17]Department of Psychology, Penn State University, University Park, PA; [18]Department of Psychiatry and Behavioral Sciences, University of California, Davis, CA; [19]School of Nursing, Virginia Commonwealth University, Richmond, VA; [20]Departments of Pediatrics, Environmental and Occupational Health Sciences, and Epidemiology, University of Washington, Seattle, WA; [21]Seattle Children's Research Institute, Seattle, WA; [22]Department of Psychiatry and Behavioral Sciences and the MIND Institute, University of California, Davis, School of Medicine, Sacramento, CA; [23]Department of Epidemiology, Dartmouth Geisel School of Medicine, Lebanon, NH; [24]Department of Pediatrics, University of Vermont Medical Center, Burlington, VT; [25]Division of Public Health and Department of Obstetrics, Gynecology, & Reproductive Biology, Michigan State University, East Lansing, MI; and [26]Center for the Study of Children at Risk, Departments of Psychiatry and Pediatrics, Alpert Medical School of Brown University and Women and Infants Hospital, Providence, RI

*See Acknowledgments for full listing of collaborators.

https://doi.org/10.1016/j.jpeds.2023.113468

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] whereas in utero exposure to individual substances, such as alcohol and marijuana, has 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 nonexposed 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 greater risk for neurodevelopmental concerns.

Using data from the Environmental influences on Child Health Outcomes (ECHO) Program, we (1) identified discrete patterns of polysubstance use during pregnancy, expecting at least 2 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

The ECHO Program

The ECHO Program consists of 69 existing pediatric cohorts across the US that focus on 5 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 use 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 comprised 10 ECHO-wide cohorts with information on prenatal substance use and child behavior from 2000 to 2020 (**Table I**). The 2195 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 to 2010, with the remaining births occurring from 2011 to 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 I**). We created binary variables (yes/no) for nicotine, alcohol, marijuana, opioid, and/or illicit drug use during pregnancy. See the **Appendix** 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 6-11 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 II** and the **Appendix** for more information. We modeled the heterogeneity of prenatal substance use using latent class

Table I. 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, No. (%)	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, No. (%)	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, No. (%)	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, No. (%)	124 (97.6%)	128 (98.5%)	925 (100%)	114 (100%)	473 (99%)	<5	<10 (100%)	77 (100%)	165 (100%)	171 (100%)	2185 (99.5%)
Less than 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 greater	114 (92%)	121 (95%)	407 (44%)	98 (86%)	210 (44%)	<5	<10 (100%)	77 (100%)	126 (76%)	148 (87%)	1309 (60%)
Marital status, No. (%)	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, No. (%)	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, No. (%)											
Self-report											
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, No. (%)	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, No. (%)	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, No. (%)	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, No. (%)	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, No. (%)	21 (17%)	31 (24%)	113 (12%)	25 (24%)	43 (13%)	0 (0%)	<5	<15 (21%)	26 (16%)	28 (16%)	304 (15%)

(*continued*)

Table I. Continued

Characteristics	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	Cohort 7	Cohort 8	Cohort 9	Cohort 10	Overall
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, y, at CBCL, No. (%)	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)

CBCL, Child Behavior Checklist.
Means and SDs are presented for continuous variables, whereas 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 were collected via self-report.

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.[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 2 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, although 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 1 of 3 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 the **Appendix** for more information. ORs and 95% 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 χ^2 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 3 latent classes also were 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 3-class solution fit the data well based on Bayesian information criterion values and the Lo-Mendell-Rubin likelihood ratio test (P = .045; **Table III**). Average posterior class probabilities ranged from 0.52 to 0.99. We described

Table II. 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, No. (%)	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)		<.001
Ethnicity/race, No. (%)	64 (100%)	145 (100%)	1975 (99.4%)	2184 (99.5%)	11 (<1%)*	
Non-Hispanic/White	38 (59%)	117 (81%)	1014 (51%)	1169 (54%)		<.001
Non-Hispanic/Black	19 (30%)	7 (5%)	648 (33%)	674 (31%)		<.001
Non-Hispanic/Asian	0 (0%)	2 (1%)	45 (2%)	47 (2%)		.374
Non-Hispanic/Other	4 (6%)	12 (8%)	105 (5%)	121 (6%)		.313
Hispanic	3 (5%)	7 (5%)	163 (8%)	173 (8%)		.21
Calendar year of child birth, No. (%)	64 (100%)	145 (100%)	1986 (100%)	2195 (100%)	0	
2001-2010	58 (91%)	119 (82%)	1176 (59%)	1353 (62%)		<.001
2011-2020	6 (9%)	26 (18%)	810 (41%)	842 (38%)		<.001
Socioeconomic statusrowhead						
Education, No. (%)	64 (100%)	143 (98.6%)	1978 (99.6%)	2185 (99.5%)	10 (<1%)*	
Less than high school	12 (19%)	30 (21%)	189 (10%)	231 (11%)		<.001
High school	26 (41%)	48 (34%)	571 (29%)	645 (30%)		.07
Some college and greater	26 (41%)	65 (45%)	1218 (62%)	1309 (60%)		<.001
Marital status, No. (%)	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%)		.407
Insurance type, No. (%)	20 (31.3%)	17 (11.7%)	1020 (51.4%)	1057 (48.2%)	1175 (53.5%)	
Any insurance	20 (100%)	17 (100%)	1015 (100%)	1052 (100%)		.913
Medicare/Medicaid	19 (95%)	8 (47%)	542 (53%)	569 (54%)		.001
Private	1 (100%)	9 (82%)	495 (94%)	505 (93%)		.291
Other	0 (0%)	0 (0%)	17 (2%)	17 (2%)		.745
No insurance	0 (0%)	0 (0%)	5 (<1%)	5 (<1%)		.913
Comorbidities						
History of depression through 8 wk postpartum, No. (%)	37 (57.8%)	106 (73.1%)	714 (36%)	857 (39%)	1338 (61.0%)	
Yes	14 (38%)	31 (29%)	132 (18%)	177 (21%)		.001
Depression during pregnancy, No. (%)	37 (57.8%)	101 (69.7%)	560 (28.2%)	698 (31.8%)	1497 (68.2%)	
Yes	14 (38%)	29 (29%)	90 (16%)	133 (19%)		<.001
Substance use during pregnancy						
Alcohol, No. (%)	64 (100%)	144 (99.3%)	1917 (96.5%)	2125 (96.8%)	70 (3.2%)*	
Yes	24 (38%)	98 (68%)	195 (10%)	317 (15%)		<.001
Nicotine, No. (%)	64 (100%)	143 (98.6%)	1943 (97.8%)	2150 (97.9%)	45 (2.1%)*	
Yes	48 (75%)	136 (95%)	181 (9%)	365 (17%)		<.001
Marijuana, No. (%)	64 (100%)	145 (100%)	1945 (97.9%)	2154 (98.1%)	41 (1.9%)*	
Yes	35 (55%)	70 (48%)	21 (1%)	126 (6%)		<.001
Any illicit drugs,† No. (%)	64 (100%)	144 (99.3%)	1960 (98.7%)	2168 (98.8%)	27 (1.2%)*	
Yes	64 (100%)	0 (0%)	0 (0%)	64 (3%)		<.001
Methamphetamine, No. (%)	56 (87.5%)	124 (85.5%)	1830 (92.1%)	2010 (91.6%)	185 (8.4%)*	
Yes	16 (29%)	0 (0%)	0 (0%)	16 (1%)		<.001
Cocaine, No. (%)	62 (96.9%)	144 (99.3%)	1964 (98.9%)	2170 (98.9%)	25 (1.1%)*	
Yes	25 (40%)	0 (0%)	0 (0%)	25 (1%)		<.001
Opioid use						
Use during pregnancy, No. (%)	64 (100%)	145 (100%)	1986 (100%)	2195 (100%)	0	
Yes	15 (23%)	20 (14%)	20 (1%)	55 (3%)		<.001
Prescription use, No. (%)	42 (65.6%)	123 (84.8%)	728 (36.7%)	893 (40.7%)	1299 (59.3%)	
Yes	7 (17%)	20 (16%)	20 (3%)	47 (5%)		<.001
Heroin, No. (%)	64 (100%)	139 (95.9%)	1857 (93.5%)	2060 (93.8%)	135 (6.2%)	
Yes	10 (16%)	0 (0%)	0 (0%)	10 (<1%)		<.001
Total number of substance use, No. (%)	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)		<.001
Any substance use	64 (100%)	142 (100%)	402 (21%)	608 (29%)		<.001
Child characteristics						
Sex, No. (%) with data	64 (100%)	145 (100%)	1986 (100%)	2195 (100%)	0	
Male	38 (59%)	74 (51%)	1074 (54%)	1186 (54%)		.532
Female	26 (41%)	71 (49%)	912 (46%)	1009 (46%)		
Child ethnicity/race, No. (%)	64 (100%)	145 (100%)	1982 (99.8%)	2191 (99.8%)	4 (<1%)*	
Non-Hispanic/White	29 (45%)	95 (66%)	888 (45%)	1012 (46%)		<.001
Non-Hispanic/Black	21 (33%)	5 (3%)	665 (34%)	691 (32%)		<.001
Non-Hispanic/Asian	0 (0%)	0 (0%)	29 (1%)	29 (1%)		.212
Non-Hispanic/Other	5 (8%)	29 (20%)	174 (9%)	208 (9%)		<.001
Hispanic	9 (14%)	16 (11%)	226 (11%)	251 (11%)		.795
Gestational age at birth, No. (%)	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)		.017
Birth weight, kg, No. (%)	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)		.109
Size for gestational age at birth, No. (%)	54 (84.4%)	124 (85.5%)	1843 (92.8%)	2021 (92.1%)	174 (7.9%)	

(*continued*)

Table II. Continued

Characteristics	Class 1 (illicit substance use)	Class 2 (licit substance use)	Class 3 (low substance use)	Overall	Missing data	*P* value
Large for gestational age	7 (13%)	13 (10%)	284 (15%)	304 (15%)		.302
Small for gestational age	7 (13%)	6 (5%)	141 (8%)	154 (8%)		.169
Child age, y at CBCL-Sch assessment, No. (%)	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)		.259

CBCL-Sch, Child Behavior Checklist, School aged version.
Means and SDs are presented for continuous variables whereas the number of observations and percent of total observations are presented for categorical variables.
*Denotes missing data that was imputed with multiple imputation.
†Includes any recreational, illicit, or street drugs, such as cocaine, heroin, methamphetamine (meth), MDMA (3,4-methylenedioxymethamphetamine; ecstasy), speed (amphetamine sulfate), acid/LSD, Special K (ketamine), and others.

the classes as an illicit substance use class (n = 64; 2.9%) with the greatest 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 = 1986; 90.5%) with either no or minimal alcohol (10%) and nicotine use (9%) identified during pregnancy (average number of substances used: M = 0.2, SD = 0.4). 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 greatest 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 2 substance use classes used more than 2 substances on average (M = 2.9, SD = 0.8; M = 2.2, SD = 0.5, 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 II and the Appendix.

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 IV). Children born to women in the licit use class had greater 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 greater, 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 greater 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 greater 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 = 0.27, 95% CI 0.13-0.56) and internalizing models (OR = 0.27, 95% CI 0.12-0.57). Married mothers (externalizing: OR = 0.04, 95% CI 0.02-0.12; internalizing: OR = 0.04, 95% CI 0.01-0.14, 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

Table III. Model fit statistics

Classes	Log likelihood	No. 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**	**.045**	**−2643.154**	**.0625**	**2.90%**
4 class	−2631.479	23	5439.919	5366.845	0.888	8.428	.1178	−2635.785	.2857	1.70%

BIC, Bayesian information criterion; *BLRT*, bootstrap likelihood ratio test; *LMR*, Lo-Mendell-Rubin likelihood ratio test; *ssaBIC*, Bayesian information criterion in subject level.
Lower values of BIC and ssaBIC indicate better model fit. Entropy greater than 0.80 indicates that there is good classification of individuals. For LMT and BLRT, a $P \leq .05$ suggests that the subsequent model provides a statistically significant improvement in model fit. The final 3-class solution accepted is shown in bold.

Table IV. Model predicted CBCL t scores by prenatal substance use latent classes and children in the borderline or clinical range

Outcomes	Full sample	Prenatal substance use latent classes			
		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 vs 2, $P = .45$ 1 vs 3, $P = .07$ 2 > 3, $P = .001$, $d = 0.64$
Borderline or clinical range, No. (%)	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 vs 2, $P = .50$ 1 > 3, $P < .001$, $d = 0.16$ 2 vs 3, $P = .14$
Borderline or clinical range, No. (%)	405 18%)	13 (20%)	36 (25%)	356 (18%)	

CBCL-Sch, Child Behavior Checklist, School-aged version.
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 χ^2 test of group difference between latent class means.

class compared with non-Hispanic/non-White mothers. Maternal age at delivery did not predict class membership for either problem behavior (Table V).

Child sex, child ethnicity/race, and maternal marital status significantly predicted externalizing behavior. Greater externalizing scores were more likely in male children ($b = 1.31$, 95% CI 0.94-1.68), non-Hispanic/White ($b = 1.37$, 95% CI 0.53-2.21) and Hispanic children ($b = 1.67$, 95% CI 0.43-2.92), and children with an unmarried mother ($b = -2.23$, 95% CI –3.56 to –0.89) than female children, non-Hispanic/non-White children, and children with married mothers. Child sex and ethnicity/race significantly predicted internalizing behavior scores. Greater 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 0.49-2.37) 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 VI).

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 = 2195) from 10 ECHO-wide cohorts who were asked about substance use during pregnancy. We identified 3 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 = 1986) had little-to-no substance use during their pregnancy. The remaining 2 classes accounted for most of the substance use in our study sample. However, the substance use—these 2 classes was unique, with one class comprising mainly illicit substance use (2.9%; n = 64)—women who primarily used illicit drugs, along with licit substances (eg, nicotine, alcohol, marijuana, and prescription

Table V. Predictors of latent class membership for each CBCL outcome model

Covariates	Illicit use vs licit use	Licit class vs low use
	OR (95% CI)	OR (95% CI)
CBCL externalizing behavior t score model		
Maternal education (greater thanhigh 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, y	1.04 (0.94, 1.15)	0.98 (0.96-1.01)
CBCL internalizing behavior t-score model		
Maternal education (greater than 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, y	1.04 (0.94-1.15)	0.98 (0.95-1.01)

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

Table VI. 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 (greater than 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, y	−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)

Bolded results are significant at $P < .05$.

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 greater than 2, 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 greater 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 (ie, several children had subclinical externalizing scores). Nevertheless, approximately 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 greater risk of developing externalizing behavior problems in middle childhood.

In contrast, children born to women belonging to the illicit use class—characterized by a greater 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, multicohort 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 greater 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. Because of the design of the study, we did not account for the postnatal caregiving environment, which can impact child behavioral outcomes. In addition, 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 3 substance use classes underscores the variations in polysubstance use profiles. Children exposed to nicotine and alcohol in utero showed greater 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 approximately 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.

Although 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 greater 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. ■

Declaration of Competing Interest

This work was supported by the Environmental influences on Child Health Outcomes (ECHO) program, Office of The Director, National Institutes of Health, under award numbers U2COD023375 (Coordinating Center), U24OD023382 (Data Analysis Center), U24OD023319 (PRO Core), 5UH3OD023320-05 (to J.A.), UG3OD023337 (to R.W.), UH3OD023268 (to Litonjua), 4UH3OD023248-03 (to D.D.), 5UH3OD023348-05 (to M.O.), 4UH3OD023328-03 (to C.D.), UH3OD023279 (to A.E.), 4UH3OD023342 (to C.N.), UH3OD023289 (to A.F., L.C.), 4UH3OD023365-03 (to I.H.), 4UH3OD023244-03 (to A.H.), 4UH3OD023275-03 (to M.K.), UH3OD023347 (to B.L.), 5TUH3OD023347 (to C.M.), UH3 OD023389 (to L.L.), UH3OD023349 (to T.O.), R01 HD 034568 and UH3OD 023286 (to E.O.), 4UH3OD023271-03 (to C.K., S.S.), UH3 OD023285 (to N.P.), and 4UH3OD023282-03 (to J.G.). The study sponsor had no role in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the manuscript for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors declare no conflicts of interest.

We thank our ECHO colleagues, the medical, nursing, and program staff, as well as the children and families participating in the ECHO cohorts. We also acknowledge the contribution of the following ECHO program collaborators:

ECHO Components—Coordinating Center: Duke Clinical Research Institute, Durham, NC: Smith PB, Newby KL; Data Analysis Center: Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD: Jacobson LP; Research Triangle Institute, Durham, NC: Parker CB; Person-Reported Outcomes Core: Northwestern University, Chicago, IL: Gershon R, Cella D.

ECHO Awardees and Cohorts—Brigham and Women's Hospital, Boston, MA: Litonjua AA; Columbia University, New York, NY: Perera FP, Herbstman JB; Dartmouth College, Hanover, NH: Karagas MR; Drexel University, Philadelphia, PA: Newschaffer CJ; George Washington University, Washington, DC: Ganiban J; Harvard Pilgrim Health Care, Inc., Canton, MA: Oken E; Icahn School of Medicine at Mount Sinai, New York, NY: Wright RJ; Kaiser Permanente, Oakland, CA: Ferrara A, Croen LA; Michigan State University, East Lansing, MI: Paneth N, Kerver JM, Ruden DM; Memorial Hospital of Rhode Island, Pawtucket, RI: Deoni S, D'Sa VA; New York State Psychiatric Institute, New York, NY: Duarte CS; New York University Langone Health, New York, NY: Blair C; Oregon Health & Science University, Portland OR: McEvoy CT; Penn State University, University Park, PA: Neiderhiser JM; University of California, San Francisco, CA: LeWinn KZ; Bush NR; University of Colorado Anschutz Medical Campus, Aurora, CO: Dabelea D; University of North Carolina, Chapel Hill, NC: O'Shea M, Fry R; University of Oregon, Eugene, OR: Leve LD; University of Pittsburgh, Pittsburgh, PA: Hipwell AE; University of Rochester, Rochester, NY: O'Connor TG; University of Tennessee Health Sciences Center, Memphis, TN: Mason A; University of Utah, Salt Lake City, UT: Stanford JB, Giardino A, Porucznik CA; University of Washington, Seattle, WA: Karr C, Sathyanarayana S; University of Wisconsin, Madison, WI: Gern J; Avera Research Institute, Sioux Falls, SD: Elliott AJ.; University of California, Davis, Sacramento, CA: Hertz-Picciotto I, Schweitzer, JB, Bennett, D.

Submitted for publication Jun 7, 2022; last revision received Mar 30, 2023; accepted Apr 21, 2023.

Reprint requests: Sarah E. Maylott, PhD, Department of Psychiatry & Behavioral Sciences, Duke University, 2400 Pratt St, Durham, NC 27705.
E-mail: sarah.maylott@duke.edu

Data Statement

Data sharing statement available at www.jpeds.com.

References

1. McCance-Katz EF. Key substance use and mental health indicators in the United States: results from the 2016 national Survey on drug Use and health. Subst Abuse Ment Health Serv Adm [Internet]; SMA 17-5044, NSDUH. 2017. Accessed May 1, 2022. https://www.samhsa.gov/data
2. Ariadna F. Substance use during pregnancy. F1000Res 2016;5. F1000 Faculty Rev-887.
3. Conradt E, Degarmo D, Fisher P, Abar B, Lester BM, Lagasse LL, et al. The contributions of early adverse experiences and trajectories of respiratory sinus arrhythmia on the development of neurobehavioral

disinhibition among children with prenatal substance exposure. Dev Psychopathol 2014;26:901-16.
4. Kocherlakota P. Neonatal abstinence syndrome. Pediatrics 2014;134:e547-61.
5. Liu J, Bann C, Lester B, Tronick E, Das A, Lagasse L, et al. Neonatal neurobehavior predicts medical and behavioral outcome. Pediatrics 2010;125:e90-8.
6. Moilanen KL, Shaw DS, Maxwell KL. Developmental cascades: externalizing, internalizing, and academic competence from middle childhood to early adolescence. Dev Psychopathol 2010;22:635-53.
7. D'Onofrio BM, Van Hulle CA, Waldman ID, Rodgers JL, Rathouz PJ, Lahey BB. Causal inferences regarding prenatal alcohol exposure and childhood externalizing problems. Arch Gen Psychiatry 2007;64:1296-304.
8. Sood B, Delaney-Black V, Covington C, Nordstrom-Klee B, Ager J, Templin T, et al. Prenatal alcohol exposure and childhood behavior at age 6 to 7 years: I. Dose–response effect. Pediatrics 2001;108:e34.
9. Cornelius MD, De Genna NM, Leech SL, Willford JA, Goldschmidt L, Day NL. Effects of prenatal cigarette smoke exposure on neurobehavioral outcomes in 10-year-old children of adolescent mothers. Neurotoxicol Teratol 2011;33:137-44.
10. Behnke M, Smith VC, Abuse C on S, Newborn C on FA. Prenatal substance abuse: short- and long-term effects on the exposed fetus. Pediatrics 2013;131:e1009-24.
11. Min MO, Minnes S, Park H, Ridenour T, Kim JY, Yoon M, et al. Developmental trajectories of externalizing behavior from ages 4 to 12: prenatal cocaine exposure and adolescent correlates. Drug Alcohol Depend 2018;192:223-32.
12. Lester BM, Bagner DM, Liu J, LaGasse LL, Seifer R, Bauer CR, et al. Infant neurobehavioral dysregulation: behavior problems in children with prenatal substance exposure. Pediatrics 2009;124:1355-62.
13. Lee SJ, Bora S, Austin NC, Westerman A, Henderson JMT. Neurodevelopmental outcomes of children born to opioid-dependent mothers: a systematic review and meta-analysis. Acad Pediatr 2020;20:308-18.
14. Paul SE, Hatoum AS, Fine JD, Johnson EC, Hansen I, Karcher NR, et al. Associations between prenatal cannabis exposure and childhood outcomes: results from the ABCD study. JAMA Psychiatr 2021;78:64-76.
15. Eze N, Smith LM, LaGasse LL, Derauf C, Newman E, Arria A, et al. School-aged outcomes following prenatal methamphetamine exposure: 7.5-year follow-up from the infant development, environment, and lifestyle study. J Pediatr 2016;170:34-8.e1.
16. de Cubas MM, Field T. Children of methadone-dependent women: developmental outcomes. Am J Orthopsychiatry 1993;63:266-76.
17. O'Connor MJ, Paley B. The relationship of prenatal alcohol exposure and the postnatal environment to child depressive symptoms. J Pediatr Psychol 2006;31:50-64.
18. Gray KA, Day NL, Leech S, Richardson GA. Prenatal marijuana exposure: effect on child depressive symptoms at ten years of age. Neurotoxicol Teratol 2005;27:439-48.
19. Conradt E, Flannery T, Aschner JL, Annett RD, Croen LA, Duarte CS, et al. Prenatal opioid exposure: neurodevelopmental consequences and future research priorities. Pediatrics 2019;144:e20190128.
20. Nygaard E, Slinning K, Moe V, Walhovd KB. Behavior and attention problems in eight-year-old children with prenatal opiate and polysubstance exposure: a longitudinal study. PLoS One 2016;11:e0158054.
21. Slinning K. Foster placed children prenatally exposed to poly-substances. Eur Child Adolesc Psychiatry 2004;13:19-27.
22. Messiah SE, Miller TL, Lipshultz SE, Bandstra ES. Potential latent effects of prenatal cocaine exposure on growth and the risk of cardiovascular and metabolic disease in childhood. Prog Pediatr Cardiol 2011;31:59-65.
23. Bennett DS, Bendersky M, Lewis M. Children's intellectual and emotional–behavioral adjustment at 4y as a function of cocaine exposure, maternal characteristics, and environmental risk. Dev Psychol 2002;38:648-58.
24. Finger B, Jobin A, Bernstein VJ, Hans S. Parenting contributors to early emerging problem behaviour in children of mothers in methadone maintenance treatment. Infant Child Dev 2018;27:e2042.
25. Romano ME, Buckley JP, Elliott AJ, Johnson CC, Paneth N. SPR perspectives: scientific opportunities in the environmental influences on child health outcomes program. Pediatr Res 2021:1-7.
26. Paneth N, Monk C. The importance of cohort research starting early in life to understanding child health. Curr Opin Pediatr 2018;30:292-6.
27. LeWinn KZ, Caretta E, Davis A, Anderson AL, Oken E. SPR perspectives: environmental influences on Child Health Outcomes (ECHO) Program: overcoming challenges to generate engaged, multidisciplinary science. Pediatr Res 2021:1-8.
28. Achenbach TM, Rescorla LA. Manual for the ASEBA school-age forms & profiles. Burlington, (VT): University of Vermont, Research Center for Children, Youth, & Families; 2000.
29. Little TD. 5 latent class analysis and finite mixture modeling. In: The Oxford handbook of quantitative methods. Oxford United Kingdom: Oxford University Press; 2013. p. 551.
30. Asparouhov T, Muthen B. Auxiliary variables in mixture modeling: using the BCH method in Mplus to estimate a distal outcome model and an arbitrary secondary model, 80. Mplus Web Notes: No. 21, Version 11.
31. Bakk Z, Tekle FB, Vermunt JK. Estimating the association between latent class membership and external variables using bias-adjusted three-step approaches. Sociol Methodol 2013;43:272-311.
32. Nylund-Gibson K, Choi AY. Ten frequently asked questions about latent class analysis. Transl Issues Psychol Sci 2018;4:440-61.
33. Nylund-Gibson K, Grimm RP, Masyn KE. Prediction from latent classes: a demonstration of different approaches to include distal outcomes in mixture models. Struct Equ Model Multidiscip J 2019;26:967-85.
34. Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: a Monte Carlo simulation study. Struct Equ Model Multidiscip J 2007;14:535-69.
35. Vermunt JK. Latent class modeling with covariates: two improved three-step approaches. Polit Anal 2010;18:450-69.
36. Muthén B, Muthén L. Mplus. In: Handbook of item response theory. Boca Raton, FL: CRC Press Taylor & Francis Group; 2017.
37. Liu Y, Williamson V, Setlow B, Cottler LB, Knackstedt LA. The importance of considering polysubstance use: lessons from cocaine research. Drug Alcohol Depend 2018;192:16-28.
38. Delano K, Gareri J, Koren G. Rates of fetal polydrug exposures in methadone-maintained pregnancies from a high-risk population. PLoS One 2013;8:e82647.
39. Khoury JE, Jamieson B, Milligan K. Risk for childhood internalizing and externalizing behavior problems in the context of prenatal alcohol exposure: a meta-analysis and comprehensive examination of moderators. Alcohol Clin Exp Res 2018;42:1358-77.
40. Knopik VS. Maternal smoking during pregnancy and child outcomes: real or spurious effect? Dev Neuropsychol 2009;34:1-36.
41. Garg M, Garrison L, Leeman L, Hamidovic A, Borrego M, Rayburn WF, et al. Validity of self-reported drug use information among pregnant women. Matern Child Health J 2016;20:41-7.
42. Yonkers KA, Howell HB, Gotman N, Rounsaville BJ. Self-report of illicit substance use versus urine toxicology results from at-risk pregnant women. J Subst Use 2011;16:372-80.
43. HEALthy Brain and child development study [Internet]. NIH HEAL Initiative. 2019. Accessed April 18, 2022. https://heal.nih.gov/research/infants-and-children/healthy-brain

Appendix

Prenatal Substance Use

Nicotine exposure was defined as cigarette smoking, use of electronic nicotine delivery devices/ENDS (e-cigarettes, vapes, vape pens), and other forms of tobacco (chewing tobacco/snuff, nicotine patch, nicotine gum/lozenges, cigar, pipe, hookah, Bidi/Beedi). Alcohol use included the consumptions of beer, wine, mixed drinks, spirits, shot liquor, or any other type of alcohol. Prescription opioid use included morphine, codeine, Percodan, OxyContin, and any other prescribed opioid medication. Illicit drug use was defined as any use of cocaine, heroin, methamphetamines, MDMA (3,4-methylenedioxymethamphetamine; ecstasy), speed (amphetamine sulfate), acid or LSD, and/or ketamine, excluding marijuana use (hash, pot, weed, ganja, blunt, cannabis, or THC [tetrahydrocannabinol]).

Maternal Demographic Information

Highest level of maternal education attained was categorized as less than high school, high school, or some college and above. Household income was categorized as <$30 000, $30 000 to $49 999, $50 000 to $74 999, $75 000 to $99 000, and $100 000 or more. Child and maternal race and ethnicity were categorized as non-Hispanic White, non-Hispanic Black, non-Hispanic other, and Hispanic. Non-Hispanic other included Asians, Alaska Native, American Indian, Native Hawaiian, and Pacific Islander. Prenatal marital status was defined as married or living with a partner or not married (widowed; separated; divorced; single, never married; partnered/boyfriend or girlfriend, not living together). Insurance type was categorized as Medicare, Medicaid, medical assistance, Children's Health Insurance Program, or any kind of state or government assistance plan based on income or disability of biological mother (yes/no); private insurance, including Tricare/military health care and Indian Health Service coverage (yes/no); other insurance (yes/no); and no insurance (yes/no).

We defined maternal history of depression as any diagnosis of depression before the pregnancy through 8 weeks postpartum by medical records, use of *International Classification of Diseases*, *Ninth* and *Tenth Revision* codes (*International Classification of Diseases*, *Ninth Revision*: 296.2X, 296.3X, 300.4, 296.9X; *International Classification of Diseases*, *Tenth Revision*: F32.XX, F33.XX, F34.1, F39.XX), and/or self-report.

Child Demographic Information

Child characteristics included calendar year of the child's birth and age at administration of the Child Behavior Checklist, School aged version and child designated sex at birth (male, female). Gestational age at birth in completed weeks and birthweight (in grams) was obtained through maternal medical records, child medical records, and/or parent-report. Large and small for gestational age at birth were defined as the 90% and 10% percentile for birth weight for gestational age, respectively.[1,2] Head circumference at birth (centimeters) and APGAR scores at 1 and 5 minutes were obtained via child medical records.

Missing Data

We used multiple imputation for missing data (**Table II**) by fully conditional specification (FCS) with a discriminant function[3] for categorical and binary variables, including race/ethnicity, maternal education, marital status, prenatal alcohol, nicotine, illicit drug, and marijuana use. We used the FCS predictive mean matching method for imputing the continuous variable of maternal age at delivery. We included prenatal substance use, child problem behavior (CBCL scores), and all the covariates in the main analysis in the imputation models, as well as Cohort-ID as a classification variable. Models presented in **Tables IV-VI** combined estimates from 25 imputations.

References

1. Grantz KL, Hediger ML, Liu D, Louis GM. Fetal growth standards: the NICHD fetal growth study approach in context with INTERGROWTH-21st and the World Health Organization Multicentre growth reference study. Am J Obstet Gynecol 2018;218:S641-55. https://doi.org/10.1016/j.ajog.2017.11.593
2. Papageorghiou AT, Kennedy SH, Salomon LJ, Altman DG, Ohuma EO, Stones W, et al. The INTERGROWTH-21st fetal growth standards: toward the global integration of pregnancy and pediatric care. Am J Obstet Gynecol 2018;218:S630-40. https://doi.org/10.1016/j.ajog.2018.01.01
3. Little TD. 5 latent class analysis and finite mixture modeling. In: . The Oxford Handbook of Quantitative Methods. Oxford, United Kingdom: Oxford University Press; 2013. p. 551.