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Assessment of Psychosocial and Neonatal Risk Factors for Trajectories of Behavioral Dysregulation Among Young Children From 18 to 72 Months of Age

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Abstract

IMPORTANCE Emotional and behavioral dysregulation during early childhood are associated with severe psychiatric, behavioral, and cognitive disorders through adulthood. Identifying the earliest antecedents of persisting emotional and behavioral dysregulation can inform risk detection practices and targeted interventions to promote adaptive developmental trajectories among at-risk children.

OBJECTIVE To characterize children's emotional and behavioral regulation trajectories and examine risk factors associated with persisting dysregulation across early childhood.

DESIGN, SETTING, AND PARTICIPANTS This cohort study examined data from 20 United States cohorts participating in Environmental influences on Child Health Outcomes, which included 3934 mother-child pairs (singleton births) from 1990 to 2019. Statistical analysis was performed from January to August 2022.

EXPOSURES Standardized self-reports and medical data ascertained maternal, child, and environmental characteristics, including prenatal substance exposures, preterm birth, and multiple psychosocial adversities.

MAIN OUTCOMES AND MEASURES Child Behavior Checklist caregiver reports at 18 to 72 months of age, with Dysregulation Profile (CBCL-DP = sum of anxiety/depression, attention, and aggression).

RESULTS The sample included 3934 mother-child pairs studied at 18 to 72 months. Among the mothers, 718 (18.7%) were Hispanic, 275 (7.2%) were non-Hispanic Asian, 1220 (31.8%) were non-Hispanic Black, 1412 (36.9%) were non-Hispanic White; 3501 (89.7%) were at least 21 years of age at delivery. Among the children, 2093 (53.2%) were male, 1178 of 2143 with Psychosocial Adversity Index [PAI] data (55.0%) experienced multiple psychosocial adversities, 1148 (29.2%) were exposed prenatally to at least 1 psychoactive substance, and 3066 (80.2%) were term-born (≥37 weeks' gestation). Growth mixture modeling characterized a 3-class CBCL-DP trajectory model: high and increasing (2.3% [n = 89]), borderline and stable (12.3% [n = 479]), and low and decreasing (85.6% [n = 3366]). Children in high and borderline dysregulation trajectories had more prevalent maternal psychological challenges (29.4%-50.0%). Multinomial logistic regression analyses indicated that children born preterm were more likely to be in the high dysregulation trajectory (adjusted odds ratio [aOR], 2.76; 95% CI, 2.08-3.65; *P* < .001) or borderline dysregulation trajectory (aOR, 1.36; 95% CI, 1.06-1.76; *P* = .02) vs low dysregulation trajectory. High vs low dysregulation trajectories were less prevalent for girls compared with boys (aOR, 0.60; 95% CI, 0.36-1.01; *P* = .05) and children with lower PAI (aOR, 1.94; 95% CI, 1.51-2.49; *P* < .001). Combined increases in PAI and

Key Points

Question Can adverse prenatal, neonatal, and psychosocial conditions identify the earliest risk factors associated with persistent behavioral and emotional dysregulation across early childhood?

Findings In this cohort study of 3934 mother-child pairs, preterm birth and the interactive influences of cumulative prenatal substance exposures and psychosocial adversities were associated with persisting high and borderline Child Behavior Checklist-Dysregulation trajectories across 18 to 72 months of age.

Meaning These findings suggest salient indicators of resilience and risk for persisting emotional and behavioral dysregulation to inform earlier and more specific behavioral screening and to target interventions with potential to promote adaptive development among at-risk children.

➕ **Supplemental content**

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

prenatal substance exposures were associated with increased odds of high vs borderline dysregulation (aOR, 1.28; 95% CI, 1.08-1.53; *P* = .006) and decreased odds of low vs high dysregulation (aOR, 0.77; 95% CI, 0.64-0.92; *P* = .005).

CONCLUSIONS AND RELEVANCE In this cohort study of behavioral dysregulation trajectories, associations were found with early risk factors. These findings may inform screening and diagnostic practices for addressing observed precursors of persisting dysregulation as they emerge among at-risk children.

Introduction

Emotional and behavioral dysregulation among school-aged children has an average multinational prevalence of 9% (range, 2%-18%; n = 56 666)[1] and is associated with subsequently severe behavioral, affective, and cognitive impairments through adulthood.[2-4] Risk factors for children's persisting emotional and behavioral dysregulation involve the cumulative burden of medical and socioeconomic adversities, as well as parental psychological and substance use challenges.[5-11]

Children born preterm (<37 weeks' gestation), and children whose parents have co-occurring psychological and substance use challenges are at elevated risk for persisting dysregulation.[12-16] Moreover, prematurity, in combination with environmental adversity has been associated with childhood anxiety, attention, mood, and social-communicative disorders that persist into adulthood.[17-19] Preterm children's outcomes differed from term-born children's outcomes,[20-22] whereas psychosocial factors were associated with behavioral dysregulation similarly across various samples.[8,23,24]

The Child Behavior Checklist (CBCL/1.5-5)[25] is a well-validated measure that yields subscores for emotional reactivity, sleep and somatic problems, social withdrawal, anxiety/depression, attention, and aggression.[26] The latter 3 subscores compose the Dysregulation Profile (CBCL-DP), a global indicator of risk for major impairments throughout adolescence and adulthood.[2,12,20,27,28] Early dysregulation expressed as difficulties with attention, emotional regulation, and social relationships has been found to persist through childhood,[15,29] with demonstrated significance identifying subsequent suicidality,[4,30] substance use,[31] attention deficits, bipolar and major depression, anxiety, and disruptive behavior disorders into adulthood.[3,4]

While prior studies have documented individual medical, economic, and social risk factors for poor behavioral regulation, less is known about the earliest risk factors associated with persisting dysregulation among US children. Thus it is important to examine behavioral trajectories in large, diverse samples with child and caregiver data that includes prenatal and neonatal exposures.

The present study was designed to address gaps regarding the earliest antecedents of persisting behavioral dysregulation across early childhood.[32] Our goals were to characterize children's CBCL-DP trajectories and identify early psychosocial and neonatal characteristics associated with resilience compared with persisting dysregulation. We hypothesized that low or improved dysregulation would be associated with more socioenvironmental resources and fewer adversities, and persisting dysregulation would be associated with more adverse perinatal, psychosocial, and environmental exposures. We examined these associations among a diverse multicohort sample of US children enrolled in the National Institutes of Health Environmental influences on Child Health Outcomes (ECHO) program[33,34] investigation of early-life exposures that affect child health and neurodevelopment.[35]

Methods

Participants

Participants included 3934 children aged 18 to 72 months born in 1990 to 2019 and enrolled in 20 ECHO cohorts (eTable 1 in Supplement 1). Inclusion criteria were: (1) singleton births; (2) data on prenatal exposure to alcohol, nicotine, marijuana, opioids, and illicit substances; and (3) CBCL/1.5-5 data[25] at ages 18 through 72 months.

For each local cohort and for ECHO, data use agreements were approved by their respective institutional review boards and written informed consent for maternal and child participation were obtained. This cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Procedures

Prenatal Substance Exposure

Prenatal substance use data (eFigure 1 in Supplement 1) was obtained from self-report, medical record abstraction, and/or biological assays[36-38]: (1) nicotine (tobacco; nicotine patch, gum, lozenges, inhaler); (2) alcohol; (3) marijuana; (4) opioids (morphine, codeine, Percodan, OxyContin, fentanyl, heroin); and (5) illicit substances (cocaine, methamphetamines, hallucinogens, inhalants; specified unprescribed or misused pharmaceutical). To quantify cumulative prenatal exposures, each category endorsed was assigned a value of 1 and the sum of each substance category used was calculated[39,40] (range: 0-5).

Socioenvironmental Characteristics

Maternal education was categorized as (1) less than high school degree, (2) high school graduate or GED, (3) some college, and (4) Bachelor's degree and above. Self-identified race and ethnicity were categorized as Hispanic, non-Hispanic American Indian or Alaska Native, non-Hispanic Asian, non-Hispanic Black, non-Hispanic Native Hawaiian or Pacific Islander, non-Hispanic White, non-Hispanic other race or ethnicity, and non-Hispanic multiple races. Race and ethnicity were collected by self-report to describe the diversity among ECHO mothers and children. Marital or partner status was defined as married or living with a partner, or not married nor partnered. Health insurance type was dichotomized as none and publicly subsidized, or private and employer-provided insurance.

Psychological History

Maternal psychological history was operationalized using data on psychiatric diagnoses and depressive symptom scores on self-reported questionnaires and/or medical records. Maternal psychological history was defined as yes if there was either a prior psychiatric diagnosis or Patient-Reported Outcomes Measurement Information System v1.0 (PROMIS)[41] depressive symptom T-score greater than or equal to 55 prior to the first CBCL assessment.

Maternal psychiatric diagnoses included major depression, dysthymia, phobias, and bipolar, anxiety, panic, obsessive-compulsive, posttraumatic stress, and attention-deficit disorders. Depressive symptoms were reported on the following standardized screening measures: (1) PROMIS v1.0[42,43]; (2) Edinburgh Postnatal Depression Scale[44]; (3) Adult Self-Report Achenbach System Depression Problems Syndrome Scale; (4) Brief Symptom Inventory; (5) Center for Epidemiological Studies Depression Scale; (6) Patient Health Questionnaire; (7) Beck Depression Inventory[45]; and (8) Kessler 6 Mental Health Scale.[46,47] Measures were harmonized using PROsetta Stone, which incorporates item response theory and equipercentile score–linking with the PROMIS Depression T-score metric (mean [SD]: 50 [10])[44] in cross-walk conversion tables. Validated PROMIS Depression thresholds have identified T-scores greater than or equal to 55 as a positive screen.[41,48]

Psychosocial Adversity Index

We created a Psychosocial Adversity Index (PAI) to quantify the cumulative burden of adverse conditions in which children were developing, assigning a value of 1 for each for the following criteria based on previously validated methods[23,49]: (1) maternal age at delivery less than 21 years; (2) maternal education less than some college (based on postrecession challenges for adults who did not attend college[9,50]); (3) publicly subsidized or no health insurance; (4) single-parent household (unmarried or not living with a partner); and (5) prior maternal psychiatric diagnosis or positive depressive symptom screen. We modeled PAI (range: 0-5) as a continuous variable.

Birth Outcomes

Gestational age (GA) groups included term (≥37 weeks), preterm (<37 weeks), moderate or late preterm (32-36 weeks), and very preterm (<32 weeks). Small-for-gestational-age (SGA; <10th percentile) and large-for-gestational-age (LGA; >90th percentile) were defined using the International Fetal and Newborn Growth Consortium for the 21st Century fetal growth standards.[51] Postnatal length of hospital stay (LOS) was calculated from dates of birth and neonatal discharge. GA-specific median LOS was determined (when continuous LOS was available); children were categorized as less than vs greater than or equal to the median GA-specific LOS as a proxy for illness severity at birth.

Child Behavior Checklist/1.5-5

Across cohort-specific 18- to 72-month assessment protocols, caregivers completed CBCLs per standardized reporting procedures,[25] with items rated: 0 = not true (as far as you know), 1 = somewhat or sometimes true, and 2 = very or often true. Subscores were calculated for emotional reactivity, sleep and somatic problems, withdrawn, anxiety/depression, attention, and aggression, and transformed into standardized T-scores (mean [SD]: 50 [10]).[25] The CBCL-DP is the sum of subscores for *Anxious/Depressed* (8 items), *Attention Problems* (5 items), and *Aggressive Behavior Problems* (19 items); scores greater than 180 defined clinically validated dysregulation using categories validated in preschool samples.[4,52]

Statistical Analysis

Univariate differences among maternal and child characteristics associated with CBCL outcomes were examined using χ^2 and *t* tests for categorical and continuous variables, respectively. Univariate and multivariable significance was set at 2-sided *P* < .05. We used growth mixture modeling (GMM) to identify mutually exclusive subpopulations' patterns of change in dysregulation from ages 18 to 72 months. Age epochs for repeated measures were 18 to 35 months, 36 to 47 months, 48 to 59 months, and 60 to 72 months. If more than 1 CBCL was available in an individual age epoch, their mean CBCL for the age epoch was calculated.

GMM, a latent variable modeling approach, estimates a categorical latent variable (class), which allows for different groups of individual growth trajectories to vary around class-specific means using repeated measures of CBCL dysregulation.[53-55] The resulting model created a single latent class, as well as class-specific latent intercepts and latent slopes. Beginning first with a single latent class, intercept, and slope, systematic iteration through models estimated increasing numbers of classes. Bayesian Information Criteria (BIC), Lo-Mendell-Rubin adjusted likelihood ratio test (LMR-LRT), and substantive interpretation identified the best-fitting model. Covariates to be used in the latent regression were included as auxiliary variables, and a new data set with posterior class probabilities, modal class assignment, and auxiliary variables specified.

Second in a 3-step approach examined the association of covariates with latent classes to account for measurement error in latent classification. This new data set was used to perform step 3: multinomial logistic regression with children nested in cohorts and adjusted for children's birth sex and year investigated trajectory class membership associations with cumulative prenatal substance exposure (continuous), PAI (continuous), and GA group (term vs preterm) to calculate odds ratios

and 95% CIs. Standard errors were adjusted for clustering at the cohort level via sandwich estimators. We assessed effect modification by including interaction terms for prenatal substance exposure with PAI, and prenatal substance exposure with GA group.

In this study, missing CBCL and covariate data reflected different cohort protocol content and ages at assessment. Multivariable analyses adjusted for cohort membership to account for these differences, and missing data was handled in 2 separate ways. During the class enumeration step, the standard full information maximum likelihood procedure[56-58] was used for participants missing CBCL-DP data for any age epoch. The full maximum likelihood procedure involves the estimation of population parameters by determining the value that maximizes the likelihood function based on the sample data included. To handle missing covariate data, multiple imputation was used based on current standards[54] for data treated as missing at random when the missing data are unrelated to the outcome of interest (ie, CBCL-DP trajectory). Multiple imputation in Mplus used Markov Chain Monte Carlo methods. All data management and analysis were performed in R statistical software version 4.1.0 (R Project for Statistical Computing, including tidyverse, data.table, mice) and Mplus version 8.8[59] (including MplusAutomation) from January to August 2022.

Results

There were 3934 mother-child pairs from 20 cohorts (eFigure 2, eTable 1 in Supplement 1) that met the inclusion criteria (**Figure 1**). Participant characteristics are summarized in **Table 1**. Among 3934 mothers, 718 (18.7%) self-identified as Hispanic, 252 (7.2%) as non-Hispanic Asian, 1220 (31.8%) as non-Hispanic Black, 12 (<0.1%) as non-Hispanic Native Hawaiian or Pacific Islander, 1412 (36.9%) as non-Hispanic White, 5 (<.01%) as non-Hispanic other races, and 165 (4.3%) as non-Hispanic multiple races. Overall, 3073 mothers (84.0%) had some college or above; 3501 mothers (89.7%) were at least 21 years of age at delivery; 28.0% (493 of 1759) were neither married nor living with a partner;

Figure 1. Flowchart for Eligibility and Selection of the Multicohort Sample of Study Participants
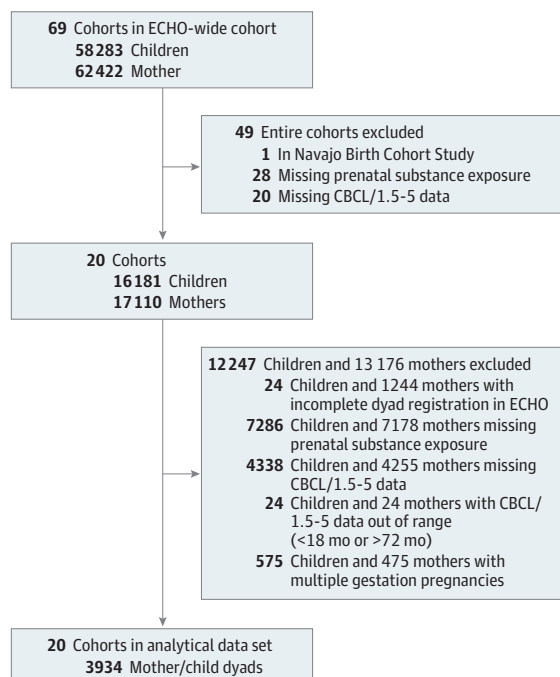
CBCL/1.5-5 indicates Child Behavior Checklist; ECHO, National Institutes of Health Environmental influences on Child Health Outcomes program.

Table 1. ECHO Multicohort Sample Characteristics

Characteristics	Study sample, No. (%)
No. of mother-child pairs	3934 (100.0)
Maternal characteristics	
Age at delivery, No. (%) with data	3903 (99.2)
<21 y	402 (10.3)
≥21 y	3501 (89.7)
Race and ethnicity, No. (%) with data	3831 (97.4)
Hispanic any race	718 (18.7)
Non-Hispanic American Indian or Alaska Native	24 (<1)
Non-Hispanic Asian	275 (7.2)
Non-Hispanic Black	1220 (31.8)
Non-Hispanic Native Hawaiian or Pacific Islander	12 (<1)
Non-Hispanic White	1412 (36.9)
Non-Hispanic self-reported other race	5 (<1)
Non-Hispanic multiple race	165 (4.3)
Highest level of education, No. (%) with data	3657 (93.0)
High school or less	584 (16.0)
Some college and above	3073 (84.0)
Some college	1158(31.7)
Bachelor's degree and above	1915 (52.4)
Marital/partner status, No. (%) with data	1759 (44.7)
Married or living with a partner	1266 (72.0)
Public/no insurance, No. (%) with data	2143 (54.5)
Yes	1303 (60.8)
History of maternal psychiatric disorder, No. (%) with data	3158 (80.3)
Yes	699 (22.1)
Maternal PROMIS depressive symptom score, No. (%) with data	2451 (62.3)
T-score, mean (min-max) [SD]	50 (33-78) [8.3]
T-score ≥55	664 (27.1)
Psychosocial Adversity Index (PAI), No. (%) with data	2143 (54.5)
PAI, mean (min-max) [SD]	1.7 (0-5) [1.2]
PAI = 0	482 (22.5)
PAI = 1	483 (22.5)
PAI = 2	589 (27.5)
PAI = 3	432 (20.2)
PAI = 4	141 (6.6)
PAI = 5	16 (<1)
Low risk (0-1)	965 (45.0)
Multirisk (2-5)	1178 (55.0)
Substance use during pregnancy, No. (%) with data	3934 (100.0)
Any substance use during pregnancy = yes	1148 (29.2)
No. of substances used, mean (min-max, SD)	0.52 (0-5, 0.86)
Alcohol	670 (17.0)
Nicotine	478 (12.2)
Marijuana	290 (7.4)
Illicit substances[a]	96 (2.4)
Any opioids	66 (1.7)

(continued)

Table 1. ECHO Multicohort Sample Characteristics (continued)

Characteristics	Study sample, No. (%)
Child characteristics	
Sex of child, No. (%) with data	3934 (100.0)
Male	2093 (53.2)
Female	1841 (46.8)
Race and ethnicity, No. (%) with data	3838 (97.6)
Hispanic any race	899 (23.4)
Non-Hispanic American Indian or Alaska Native	20 (<1)
Non-Hispanic Asian	190 (5.0)
Non-Hispanic Black	1156 (30.1)
Non-Hispanic Native Hawaiian or Pacific Islander	6 (<1)
Non-Hispanic White	1218 (31.7)
Non-Hispanic self-reported other race	5 (<1)
Non-Hispanic multiple race	344 (9.0)
Calendar year of childbirth, No. (%) with data	3934 (100.0)
Before 2005	184 (4.7)
2005-2010	1096 (27.9)
2011-2015	1765 (44.9)
2016-2019	889 (22.6)
Gestational age in weeks, No. (%) with data	3825 (97.2)
Mean (min-max) [SD]	37 (22-43) [4.4]
Term (≥37 weeks)	3066 (80.2)
Preterm (<37 weeks)	759 (19.8)
Moderate or late preterm (32-36 weeks)	243 (6.4)
Very preterm (22-31 weeks)	516 (13.5)
Large or small for gestational age, No. (%) with data	3762 (95.6)
Small for gestational age	301 (8.0)
Large for gestational age	471 (12.5)
Head circumference at delivery in cm, No. (%) with data	3135 (79.7)
Mean (min-max) [SD]	32 (18-40) [4]
APGAR scores at 1 min after birth, No. (%) with data	2989 (76.0)
Mean (min-max) [SD]	7.5 (0-10) [2]
APGAR scores at 5 min after birth, No. (%) with data	3000 (76.3)
Mean (min-max) [SD]	8.5 (0-10) [1.3]
Length of hospital stay, No. (%) with data	3142 (79.9)
Mean (min-max) [SD]	36 (0-418) [51]
<1 day	76 (2.4)
≥1 and ≤4 days	2384 (75.9)
>5 days	682 (21.7)

Abbreviations: APGAR, Appearance, Pulse, Grimace, Activity, and Respiration test; max, maximum; min, minimum; PAI, Psychosocial Adversity Index; PROMIS, Patient-Reported Outcomes Measurement Information System.

[a] Illicit substances: cocaine, heroin, methamphetamines, hallucinogens, inhalants, or any specified use of unprescribed or misused pharmaceutical (eg, amphetamines, benzodiazepines, ketamine).

60.8% (1303 of 2143) had publicly subsidized or no health insurance. Approximately one-fourth of mothers had a prior psychiatric diagnosis (699 mothers [22.1%]) or positive depressive screen (664 mothers [27.1%]), and 1178 of 2143 with data (55.0%) were in the multirisk PAI group (PAI score = 2-5; eTable 4 in Supplement 1 presents differences in PAI risk factors).

Among 3934 children, 2093 (53.2%) were male; 3066 (80.2%) were term-born (≥37 weeks); 243 (6.4%) were moderate/late preterm (32-36 weeks); 516 (13.5%) were very preterm (<32 weeks); and 2990 (79.5%) had appropriate birthweight for gestational age. Child and maternal race and ethnicity frequencies were similar to each other, with more children reported as multiple races. Patterns of prenatal substance exposures (eFigure 1 in Supplement 1) indicated 1148 (29.2%) were exposed to at least 1 substance: alcohol (17.0%), nicotine (12.2%), marijuana (7.4%), opioids (1.7%), and illicit substances (2.4%); 23.6% were exposed to 2 or more substances.
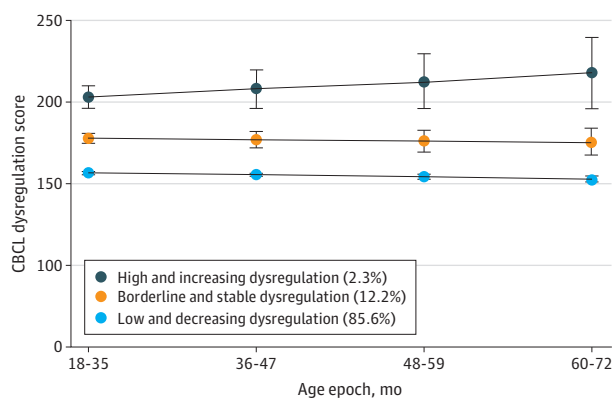
CBCL-DP Trajectories

Among 7516 CBCLs for 3934 children, 1930 children had 1 CBCL; 1267 children had 2 CBCLs; 399 children had 3 CBCLs; and 338 children had 4 or more CBCLs due to differences in cohort-specific protocols.

GMM procedures characterized CBCL-DP trajectories across age epochs, where BIC and LMR-LRT (eTable 2 in Supplement 1) indicated a 3-class solution fit the data best. Three-class model entropy was 0.92; mean posterior class probabilities ranged from 0.89 to 0.95. **Figure 2** illustrates CBCL-DP trajectory classes: (1) high and increasing dysregulation (n = 89; 2.3%); (2) borderline and stable dysregulation (n = 479; 12.3%); and (3) low and decreasing dysregulation (n = 3366; 85.6%).

CBCL-DP and Subscores Among Trajectory Classes

Overall, 10.3% (n = 405) of CBCL-DP scores were in the clinical range (mean [range], 158.6 [150-262]). **Table 2** indicates that children in the high and borderline dysregulation trajectories also had higher subscores for all 3 CBCL-DP components (attention, anxiety/depression, and aggression), and scores in the clinical range for emotional reactivity, withdrawn, somatic, and sleep problems on at least 1 assessment across 18 to 72 months of age.

Figure 2. Growth Mixture Modeling Results: Trajectories of Child Behavior Checklist (CBCL)-Dysregulation Profiles From 18 to 72 Months of Age

Test statistics for the 3-class model in eTable 2 are available in Supplement 1. A total of 7516 CBCL-Preschool parent-reports were obtained among 3934 children; 1930 children had 1 CBCL record; 1267 children had 2 CBCL records; 399 children had 3 CBCL records; and 338 children had 4 or more CBCL records. Error bands represent 95% CIs.

Table 2. Maternal and Child Characteristics Among Child Behavior Checklist Dysregulation Profile Trajectory Classes

Characteristics	No. (%)			P value
	Class 1: High and increasing DP	Class 2: Borderline and stable DP	Class 3: Low and decreasing DP	
No. of mother-child pairs	89 (2.3)	479 (12.2)	3366 (85.6)	
Maternal characteristics				
Age at delivery, No. (%) with data	88 (99.0)	470 (98.1)	3345 (99.0)	
<21 y	11 (12.5)	59 (12.6)	332 (9.9)	.83
≥21 y	77 (87.5)	411 (87.4)	3013 (90.1)	
Highest level of education, No. (%) with data	83 (93.3)	437 (91.2)	3137 (93.2)	
High school or less	26 (31.3)	116 (26.5)	442 (14.1)	<.001
Some college and above	57 (68.7)	321 (73.5)	2695 (85.9)	
Marital/partner status, No. (%) with data	49 (55.1)	235 (49.1)	1475 (43.8)	
Married or living with a partner	23 (46.9)	154 (65.5)	1089 (73.8)	<.001
Public/no insurance, No. (%) with data	58 (65.2)	296 (61.8)	1789 (53.1)	
Yes	51 (87.9)	215 (72.6)	1037 (58.0)	<.001
History of maternal psychiatric disorder, No. (%) with data	64 (71.9)	381 (79.5)	2713 (80.6)	
Yes	32 (50.0)	112 (29.4)	555 (20.5)	<.001
Maternal PROMIS depressive symptom score, No. (%) with data	64 (71.9)	336 (70.1)	2051 (60.9)	
Mean (min-max) [SD]	52 (39-76) [8.7]	53 (33-78) [8.8]	50 (33-76) [8.1]	<.001
T-score ≥55	25 (39.1)	139 (41.4)	500 (24.4)	<.001
Psychosocial Adversity Index score, No. (%) with data	58 (65.2)	296 (61.8)	1789 (53.1)	
Mean (min-max) [SD]	2.8 (1-5) [1]	2.1 (0-5) [1.2]	1.6 (0-5) [1.2]	<.001
Low (0-1)	8 (13.8)	85 (28.7)	872 (48.8)	<.001
Multirisk (2-5)	50 (86.2)	211 (71.3)	917 (51.3)	
Substance use during pregnancy, No. (%) with data	89 (100.0)	479 (100.0)	3366 (100.0)	
Any substance use during pregnancy = yes	34 (38.2)	142 (29.6)	972 (28.9)	.93
No. of substances used, mean (min-max) [SD]	0.51 (0-4) [0.82]	0.53 (0-4) [0.87]	0.52 (0-5) [0.86]	.90
Alcohol	14 (15.7)	59 (12.3)	597 (17.7)	<.001
Nicotine	21 (23.6)	75 (15.7)	382 (11.3)	.01
Marijuana	6 (6.7)	43 (9.0)	241 (7.2)	.13
Illicit substances[a]	<5	<20 (<5)	77 (2.3)	.28
Any opioids	<5	<15 (<5)	50 (1.5)	.04
Child characteristics				
Sex of child assigned at birth, No. (%) with data	89 (100.0)	479 (100.0)	3366 (100.0)	
Male	57 (64.0)	276 (57.6)	1760 (52.3)	<.001
Female	32 (36.0)	203 (42.4)	1606 (47.7)	
Gestational age (GA) in weeks, No. (%) with data	87 (100)	471 (100)	3267 (100)	
Term (≥37 wk)	48 (55.2)	346 (73.5)	2672 (81.8)	
Preterm (<37 wk)	39 (44.8)	125 (26.5)	595 (18.2)	
Very preterm (22-31 wk)	32 (36.8)	94 (20.0)	390 (11.9)	<.001
Moderate/late preterm (32-36 wk)	7 (8.0)	31 (76.6)	205 (6.3)	
Length of hospital stay, No. (%) with data	73 (82.0)	377 (78.7)	2692 (80.0)	
<1 d	0	6 (1.6)	70 (2.6)	NA
≥1 d to ≤4 d	34 (46.6)	267 (70.8)	2083 (77.4)	NA
>5 d	39 (53.4)	104 (27.6)	539 (20.0)	NA
Mean (min-max) [SD], d	65 (1-183) [52]	52 (0-269) [55]	32 (0-418) [49]	<.001

(continued)

Table 2. Maternal and Child Characteristics Among Child Behavior Checklist Dysregulation Profile Trajectory Classes (continued)

Characteristics	No. (%)			P value
	Class 1: High and increasing DP	Class 2: Borderline and stable DP	Class 3: Low and decreasing DP	
Length of hospital stay, No. (%) with data	48 (53.9)	222 (46.3)	1491 (44.3)	NA
≥37 wk	16 (33.3)	126 (56.8)	1033 (69.3)	
<median	5 (31.3)	26 (20.6)	173 (16.8)	.12
>median	11 (68.8)	100 (79.4)	860 (83.3)	
32 < GA < 36 wk	<5	<10 (<5)	88 (5.9)	
<median	0	5	35 (39.8)	.001
>median	<5	<5	53 (60.2)	
22 < GA < 32 wk	30 (62.5)	89 (40.1)	370 (24.8)	
<median	8 (26.7)	45 (50.6)	175 (47.3)	.004
>median	22 (73.3)	44 (49.4)	195 (52.7)	
Child Behavior Checklist/1.5-5 y measures[b]				
Dysregulation Profile, No. (%) with data	89 (100.0)	479 (100.0)	3366 (100.0)	
Dysregulation Profile score mean (min-max) [SD]	205 (150-256) [21]	176 (150-262) [13]	155 (150-213) [6.8]	NA
Dysregulation Profile score in the clinical range >180, No. (%)	89 (100.0)	260 (54.3)	56 (1.7)	NA
Child Behavior Checklist/1.5-5 y Symptom Subscores				
Anxious/depressed, No. (%) with data	89 (100.0)	479 (100.0)	3366 (100.0)	
Mean (min-max) [SD]	63 (50-96) [9.7]	56 (50-96) [6.4]	51 (50-70) [2.8]	NA
Borderline or clinical range, No. (%)	54 (60.7)	102 (21.3)	41 (1.2)	NA
Attention problems, No. (%) with data	89 (100.0)	479 (100.0)	3366 (100.0)	
Mean (min-max) [SD]	69 (50-80) [7.6]	61 (50-80) [7.1]	52 (50-77) [3.8]	NA
Borderline or clinical range, No. (%)	77 (86.5)	218 (45.5)	133 (4.0)	NA
Aggressive problems, No. (%) with data	89 (100.0)	479 (100.0)	3366 (100.0)	
Mean (min-max) [SD]	73 (50-100) [12]	59 (50-91) [6.8]	51 (50-93) [3]	NA
Borderline or clinical range, No. (%)	78 (87.6)	152 (31.7)	38 (1.1)	NA
Emotionally reactive, No. (%) with data	89 (100.0)	479 (100.0)	3366 (100.0)	
Mean (min-max) [SD]	67 (50-97) [10]	58 (50-93) [7]	52 (50-83) [3.8]	NA
Borderline or clinical range, No. (%)	75 (84.3)	173 (36.1)	138 (4.1)	NA
Somatic complaints, No. (%) with data	89 (100.0)	479 (100.0)	3366 (100.0)	
Mean (min-max) [SD]	59 (50-92) [9.3]	55 (50-84) [6.6]	52 (50-78) [4.4]	NA
Borderline or clinical range, No. (%)	35 (39.3)	103 (21.5)	219 (6.5)	NA
Withdrawn, No. (%) with data	89 (100.0)	479 (100.0)	3366 (100.0)	
Mean (min-max) [SD]	67 (50-91) [11]	59 (50-94) [8]	53 (50-88) [4.8]	NA
Borderline or clinical range, No. (%)	57 (64.0)	155 (32.4)	183 (5.4)	NA
Sleep problems, No. (%) with data	89 (100.0)	479 (100.0)	3366 (100.0)	
Mean (min-max) [SD]	63 (50-100) [12]	57 (50-94) [7.4]	53 (50-88) [4.6]	NA
Borderline or clinical range, No. (%)	40 (44.9)	76 (15.9)	130 (3.9)	NA

Abbreviations: DP, dysregulation profile; max, maximum; min, minimum; NA, not applicable.

[a] Illicit substances: cocaine, heroin, methamphetamines, hallucinogens, inhalants, or any specified use of unprescribed or misused pharmaceutical (eg, amphetamines, benzodiazepines, ketamine).

[b] If more than 1 CBCL was available within age epochs, all available information was used, and scores were averaged within epochs.

Maternal and Child Characteristics Among CBCL-DP Trajectory Classes

High and borderline dysregulation was more prevalent among boys vs girls, and among preterm vs term-born children (Table 2). The high dysregulation class had the highest exposure to at least 1 substance (38.2% [n = 34]) and to nicotine (23.6% [n = 21]). Alcohol exposure was highest in the low dysregulation class; patterns of marijuana, opioid, and illicit substance exposure were similar among classes.

Mean (SD) PAI scores were highest in the high dysregulation class (2.8 [1]) compared with the borderline (2.1 [1.2]) and low (1.6 [1.2]) dysregulation classes (P < .001). Compared with high and borderline dysregulation classes, children in the low dysregulation class were more likely to have

mothers who had some college education, private health insurance, and were married or living with a partner. Compared with children in the low dysregulation class, children in the high and borderline dysregulation classes had more prevalent maternal psychiatric diagnoses and positive depression screens. Furthermore, prior psychiatric diagnoses ranged from 19.4% to 50.0% among mothers who used 1 psychoactive substance during pregnancy compared with 16.1% among mothers who did not use any substance (eTable 3 in Supplement 1).

Multivariable Associations with Dysregulation Trajectory Classes

Multinomial logistic regression results (**Table 3**) for whether girls were less likely than boys to be in the high and borderline vs the low dysregulation trajectory were not statistically significant (high vs low: adjusted odds ratio [aOR], 0.60; 95% CI 0.36-1.01; P = .05; borderline vs low: aOR, 0.78; 95% CI, 0.59-1.03; P = .09). Compared with the low dysregulation trajectory, preterm children were more likely to be in the high (high vs low: aOR, 2.76; 95% CI, 2.08-3.65; P < .001) and borderline (borderline vs low: aOR, 1.36; 95% CI, 1.06-1.76; P = .02) dysregulation trajectory and less likely to be in the high vs borderline trajectory (aOR, 0.49; 95% CI, 0.36-0.68; P < .001). Increasing PAI was associated with membership in the high (aOR, 1.94; 95% CI, 1.51-2.49; P < .001) and borderline (aOR, 1.45; 95% CI, 1.32-1.60; P < .001), as well as lower odds of membership in the borderline vs high dysregulation trajectory (aOR, 0.49; 95% CI, 0.36-0.68; P < .001).

Prenatal substance exposure was not significantly associated with dysregulation trajectory class. However, increasing PAI coupled with increasing prenatal substance exposure was associated with increased odds of membership in the high vs borderline trajectory (aOR, 1.28; 95% CI, 1.08-1.53; P = .006) and decreased odds of membership in the low trajectory (aOR, 0.77; 95% CI, 0.64-0.92; P = .005). Dysregulation trajectories were not significantly associated with interactions involving GA group.

Table 3. Multivariable Analyses of Child Behavior Checklist-DP Trajectory Classes[a]

Variable	Class 2 on class 1: borderline and stable DP vs high and increasing DP		Class 1 on class 3: high and increasing DP vs low and decreasing DP		Class 2 on class 3: borderline and stable DP vs low and decreasing DP	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Model 1						
Female child sex	1.30 (0.78-2.18)	.32	0.60 (0.36-1.01)	.05	0.78 (0.59-1.03)	.09
Prenatal substance exposure	0.95 (0.71-1.26)	.71	1.1 (0.93-1.3)	.29	1.04 (0.84-1.29)	.73
PAI	0.75 (0.6-0.94)	.01	1.94 (1.51-2.49)	<.001	1.45 (1.32-1.6)	<.001
Preterm birth	0.49 (0.36-0.68)	<.001	2.76 (2.08-3.65)	<.001	1.36 (1.06-1.76)	.02
Model 2						
Female child sex	1.28 (0.77-2.12)	.34	0.61 (0.37-1.01)	.06	0.78 (0.59-1.04)	.09
Prenatal substance exposure	0.44 (0.24-0.8)	.007	2.43 (1.41-4.19)	.001	1.07 (0.63-1.81)	.79
PAI	0.67 (0.55-0.81)	<.001	2.19 (1.75-2.75)	<.001	1.46 (1.32-1.62)	<.01
Preterm birth	0.49 (0.36-0.67)	<.001	2.78 (2.11-3.65)	<.001	1.36 (1.05-1.77)	.02
PAI × prenatal substance exposure	1.28 (1.08-1.53)	.006	0.77 (0.64-0.92)	.005	0.99 (0.86-1.13)	.84
Model 3						
Female child sex	1.30 (0.78-2.18)	.31	0.60 (0.36-1.01)	.05	0.78 (0.59-1.03)	.09
Prenatal substance exposure	0.92 (0.55-1.56)	.77	1.10 (0.83-1.46)	.50	1.02 (0.76-1.36)	.89
PAI	0.75 (0.6-0.94)	.01	1.94 (1.51-2.49)	<.001	1.45 (1.32-1.6)	<.001
Preterm birth	0.48 (0.37-0.62)	<.001	2.77 (2.12-3.63)	<.001	1.33 (1.03-1.72)	.03
Preterm birth × prenatal substance use	1.07 (0.58-1.97)	.84	0.99 (0.68-1.46)	.97	1.06 (0.81-1.39)	.67

Abbreviations: DP, dysregulation profile; OR, odds ratio; PAI, Psychosocial Adversity Index.

[a] Adjusted ORs (95% CI) are displayed for the associations between prenatal substance use (continuous), PAI (continuous), and GA group at birth (term vs preterm birth) with membership in each trajectory group. Interactions terms are also included. Analyses nested children in cohorts and adjusted for child sex (reference = male sex) and child birth year; sample and cell sizes did not permit the simultaneous testing of multiple interaction terms.

Discussion

In this large, diverse US sample, we identified early and potentially modifiable risk factors associated with persisting behavioral and emotional dysregulation, including preterm birth and combined prenatal substance exposures and psychosocial adversities. Among children born preterm, increasing lengthier neonatal hospitalization, an indicator of more severe illness, was associated with persisting dysregulation.

Extending prior work, behavioral and emotional resilience was evident in 85.6% of children who exhibited low and decreasing dysregulation. Importantly, half of these children were developing in families facing multiple psychosocial adversities, and 1.2% to 6.5% had various CBCL subscores in the borderline or clinical range (Table 2). Despite their multiple challenges, these children were found to have low and decreasing dysregulation compared with children with similar risk exposures in the high and borderline trajectories.

Additional risk for persisting dysregulation was evident in the 54.3% of children in the borderline dysregulation trajectory, whose scores were in the clinical range and the maximum score exceeded the high dysregulation class maximum. These scores suggest the importance of early behavioral screening and diagnostic services to identify extremes in specific domains for targeting interventions. Clinical referral thresholds were indicated by CBCL-DP T-scores greater than 180 and T-scores greater than 65 for emotional reactivity, withdrawn, somatic, and sleep problems on at least 1 assessment, reflecting potentially modifiable precursors of persisting dysregulation.[60,61]

In this study, CBCL-DP associations with prematurity are comparable to prior studies using similar measures related to behavioral problems at 6 to 19 years.[20,22,62] Across GA groups, our results are also consistent with multinational findings regarding CBCL-DP trajectories associated with individual psychosocial adversities.[11,17,29]

Previous findings have varied depending on substance exposures, risk factors, and covariates included in multivariable models. Earlier work using confirmed frequency, timing, duration, and/or toxicological exposure measures reported greater CBCL problems associated with opioid,[14] cocaine,[16] marijuana,[63] nicotine,[64] alcohol,[65,66] and polysubstance exposures.[67,68] The finding that alcohol exposure was unexpectedly highest in the low dysregulation class warrants further study, where frequency, timing, and duration can be examined precisely for all exposures used.[6]

Importantly, high and borderline dysregulation trajectories were more prevalent among children with combined increases in both prenatal substance exposures and psychosocial adversities. Mothers with any psychological history had increased substance use and psychosocial adversities; prior diagnoses were most prevalent among those who used opioids or illicit substances (eTables 3 and 4 in Supplement 1). This combination of substance use and psychosocial adversities represents a subset of pregnant individuals who may benefit from high-quality, accessible diagnostic and targeted intervention services, ideally beginning with preconception care.[69,70]

In summary, our findings address gaps by specifying early risk factors and the antecedent behavioral problems associated with long-term dysregulation. Risk and protective factors identified here can be ascertained prenatally, at birth, and prior to postnatal discharge to the home community to individualize family supports.[71,72] When initiated earlier, behavioral and emotional interventions are more effective,[73-77] with potential to prevent escalation among children with borderline symptoms. Toward the goal of disrupting persisting dysregulation and facilitating resilience, the cumulative risks and behavioral indicators identified inform best practices and future research.

Strengths and Limitations

Study strengths include the large, diverse multicohort sample, with rigorously selected measures and data collection procedures implemented ECHO-wide to examine multiple characteristics of children, families, and environments. Importantly, 92.8% of cohort parents consented to ECHO; 7.2% refused, aged out, or were unreachable. Similarly impressive is the low 1.3% active withdrawal rate.

While maternal and environmental characteristics across the study period would be useful to study in future work, our focus was on the earliest and most salient risk factors to best inform preventive and targeted screening and intervention practices. We therefore used repeated CBCL measures to strengthen screening specificity by documenting antecedents of persisting dysregulation trajectories reflected in CBCL subscores.[60,61] Furthermore, our findings include early risk factors for persisting dysregulation among young US children with highly diverse family and health backgrounds.

This study also had limitations. Despite evidence of reliable self-reporting and convergence with bioassays,[36-38] limitations are the likely underreporting of substance exposures and the absence of quantified frequencies, durations, and amounts. Missing covariates due to cohort data collection variations required mitigation by imputation, and LOS among preterms was used as an informative proxy for neonatal illness severity indicated by extended stays.

Conclusions

This cohort study identified antecedents associated with resilience and risk in dysregulation pathways across the first 6 years of life. These findings warrant support for children with early indicated needs for monitoring and targeted interventions to address risk for persisting dysregulation.[78,79]

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SUPPLEMENT 1.
eFigure 1. Prenatal Single Substance and Polysubstance Exposure Patterns Among ECHO Children
eFigure 2. Distribution of ECHO Cohorts' Participant Recruitment Sites Across the United States
eTable 1. Cohort Characteristics
eTable 2. Growth Mixture Modeling Fit Statistics
eTable 3. Prenatal Substance Use Among Mothers With Prior Psychiatric Diagnosis and Positive PROMIS Depression Screen
eTable 4. Distribution of Psychosocial Adversity Index Variables Among Mothers With Versus Without a Prior Psychiatric Diagnosis and/or Positive Depressive Symptom Screen

SUPPLEMENT 2.
Nonauthor Collaborators

SUPPLEMENT 3.
Data Sharing Statement