Protective Factors Can Mitigate Behavior Problems After Prenatal Cocaine and Other Drug Exposures

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KEY WORDS

behavior problems, cumulative risks, prenatal cocaine exposure, protective factors

ABBREVIATIONS

CBCL—Child Behavior Checklist

DCC—data coordinating center

LGC—latent growth curve

OD—other drugs

PCE—prenatal cocaine exposure

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WHAT'S KNOWN ON THIS SUBJECT: Prenatal cocaine exposure is associated with the trajectories of childhood behavior problems. Exposure effects may also be related to maternal use of other substances during pregnancy, and risk factors other than prenatal exposure may augment the detrimental cocaine effects.

WHAT THIS STUDY ADDS: The balance between cumulative risk and protective indexes predicts behavior outcomes, independent of prenatal drug exposure. A high protective index even with a high level of risks can mitigate the detrimental effects of drug exposure on behavior problem trajectory.

abstract

BACKGROUND: We determined the role of risk and protective factors on the trajectories of behavior problems associated with high prenatal cocaine exposure (PCE)/polydrug exposure.

METHODS: The Maternal Lifestyle Study enrolled 1388 children with or without PCE, assessed through age 15 years. Because most women using cocaine during pregnancy also used other substances, we analyzed for the effects of 4 categories of prenatal drug exposure: high PCE/other drugs (OD), some PCE/OD, OD/no PCE, and no PCE/no OD. Risks and protective factors at individual, family, and community levels that may be associated with behavior outcomes were entered stepwise into latent growth curve models, then replaced by cumulative risk and protective indexes, and finally by a combination of levels of risk and protective indexes. Main outcome measures were the trajectories of externalizing, internalizing, total behavior, and attention problems scores from the Child Behavior Checklist (parent).

RESULTS: A total of 1022 (73.6%) children had known outcomes. High PCE/OD significantly predicted externalizing, total, and attention problems when considering the balance between risk and protective indexes. Some PCE/OD predicted externalizing and attention problems. OD/no PCE also predicted behavior outcomes except for internalizing behavior. High level of protective factors was associated with declining trajectories of problem behavior scores over time, independent of drug exposure and risk index scores.

CONCLUSIONS: High PCE/OD is a significant risk for behavior problems in adolescence; protective factors may attenuate its detrimental effects. Clinical practice and public health policies should consider enhancing protective factors while minimizing risks to improve outcomes of drug-exposed children. *Pediatrics* 2012;130:e1479–e1488

Reports on long-term effects of prenatal cocaine exposure (PCE) indicate an association between PCE and behavior problems, including inattention and early onset of substance use.^{1–5} Studies also show that PCE effects are related to levels of exposure.^{5,6} In addition, the detrimental effects of high PCE on externalizing behavior problems remains through age 13 years after controlling for other factors.⁷

Investigations have also found that effects noted after PCE are related to maternal or environmental factors.^{6,8–12} In addition, gender seems to moderate the PCE effects on behavior outcomes.^{4,13–15} Imaging studies suggest that PCE has a long-term effect on white matter integrity and brain volumes (ie, a decrease in cortical brain volume). However, these changes are interacting with other drug effects.^{16,17} Indeed, in human studies, it is difficult to differentiate the prenatal cocaine effects from other drugs (OD). Women using cocaine during pregnancy are more likely to use OD, illegal or legal.^{12,18,19} Each of these drugs could alter in utero programming of brain development, contributing to later behavioral outcomes.

In addition, postnatal environment and early childhood experiences may influence behavior^{8–10} with or without prenatal drug exposure.^{20,21} These factors include postnatal drug exposures, child's exposure to violence, and caretaker psychopathology.^{3,5,6,22} However, in addition to the risks for disruptive behavior,¹ any long-term effect of PCE may be offset or compensated by resilience and protective factors. Hence, the balance between risk and protective factors needs consideration in determination of PCE effects.

We therefore assessed whether the effects of high levels of PCE/polydrug exposure on childhood behavior will persist through adolescence. We also determined the roles of risk and protective factors on the trajectories of

behavior outcomes in the presence of PCE and other prenatal drug exposure. Our hypothesis was that the detrimental effects of high PCE/polydrug exposure on the trajectories of behavior problems will persist through adolescence. We further hypothesized that risk conditions will have cumulative effects on behavior outcomes while protective factors will attenuate severity of behavioral alterations in PCE/polydrug exposure.

METHODS

The Maternal Lifestyle Study, a longitudinal cohort study, assessed outcomes of children with prenatal cocaine or opiate exposure in 4 centers, with a Statistics–Data Coordinating Center (DCC) and a Neurobehavioral Battery Center.^{23,24} Each site had approval from the institutional review board and held a certificate of confidentiality issued from the National Institute on Drug Abuse. The biological parent gave written consent for study enrollment; older children later gave assent. Selection of subjects for follow-up occurred at birth between 1993 and 1995.²⁴ Exposed children were born to mothers who admitted to cocaine or opiate use or had positive meconium assays for cocaine or opiate metabolites. Nonexposed comparison children were chosen within site, matched by gestational age, gender, race, and ethnicity. Longitudinal follow-up began at the visit at age 1 month, adjusted for preterm birth.

PCE was categorized into high, some, and no exposure. High PCE referred to use ≥ 3 times per week in the first trimester, and some cocaine use referred to any other use.^{25–27} Because most women using cocaine during pregnancy are also using marijuana, opiates, alcohol, tobacco, or OD,^{12,18,19} 4 categories of drug use during pregnancy were created: high PCE with other drug exposure (high PCE/OD), some PCE/OD, no PCE but exposure to

OD (PCE–/OD+), and those with neither PCE nor OD exposure (PCE–/OD–). This categorization provides a practical approach for PCE because most cocaine users are polydrug users. Other investigators have used similar exposure groups but without levels of PCE.^{28,29}

We also selected child, family, and community factors that have been reported as added risks or may be protective against behavior problems.^{7–9,29–32} Table 1 shows the risk and protective factors. From these factors, the final variables in the growth curve models were derived. Male gender has been associated with increased risk for externalizing behavior.^{13,15,33} Smaller head circumference referred to birth measurement below the 25th percentile. BMI was calculated at each visit from child measurements; high BMI or obesity has been related to childhood and adolescent behavior outcomes.^{34,35} The verbal and full IQ were derived from the Wechsler Abbreviated Scale of Intelligence (Pearson Education, Inc, San Antonio, TX).³⁶ During each visit, the caretakers were interviewed regarding their current use of tobacco, alcohol, and marijuana; experience of domestic violence; and child protective services involvement (eg, child abuse).³⁷ To assess caretaker depression, the Beck Depression Inventory was administered,^{38,39} and for caretaker anxiety and psychological symptoms, the Brief Symptom Inventory was used.⁴⁰ We determined exposure to violence by using A Survey of Community Violence.⁴¹

Child resilience is a domain from the Child Health and Illness Profile–Adolescent Edition (The Johns Hopkins University, Baltimore, MD).⁴² From the Strange Situation procedure⁴³ at 18 months, we noted whether caretaker–child attachment was secure.²⁷ The Home Observation and Monitoring of Environment survey⁴⁴ indicated the quality of the home as observed during home visits.

TABLE 1 Potential Risk and Protective Factors and at What Ages Assessments Were Completed

Factor	Age at Assessment
Risk factors	
Child	
Prenatal drug exposure ^a	Birth
Gender ^a	Birth
Birth head circumference	Birth
Low verbal IQ ^a	9 and 13 y
Low full IQ	9 and 13 y
BMI (overweight/obese)	2–15 y
Family	
Caretaker depression ^a	4 and 30 mo, 4, 5.5, 7, 9, 11, 13, and 15 y
Caretaker psychological symptoms ^a	5 and 30 mo, 5.5, 9, and 11 y
Caretaker abuse	All years
Child abuse ^a	All years
Postnatal alcohol use ^a	All years
Postnatal tobacco use ^a	All years
Postnatal marijuana use	All years
Community	
Community violence	9, 12, and 15 y
Protective factors	
Child	
Resilience ^a	11–15 y
Family	
Secure attachment	18 mo
Home environment	5.5, 9, and 13 y
Caretaker involvement ^a	11–15 y
Caregiver supervision	12–15 y
SES ^b	All years
Family support	5.5 and 9 y
Family resources ^a	5.5 and 9 y
Community	
Neighborhood environment	9 y
No. of friends ^{a,c}	11–15 y
Extracurricular activities	9–12 and 14 y

SES, socioeconomic.

^a Included in final models.^b Five levels (index of social position).^c 1 = none, 2 = few, 3 = some, 4 = many, 5 = very many.

From the Child Health and Illness Profile–Parent report,⁴⁵ we derived the scores for caretaker involvement and the child's number of friends. The Supervision Questionnaire–Primary Caretaker⁴⁶ was used to assess facets of parental supervision and knowledge of youth's whereabouts. Information was obtained on employment, household income, and other socioeconomic status variables to derive the Hollingshead Index of Social Position.^{47–49} The Family Support Scale and the Family Resource Scale⁵⁰ were used to assess social support and basic resources available to the family. The Neighborhood Scale⁵¹ had questions on probability of success of those in the neighborhood, problems, and services. We interviewed care-

takers about the child's participation in school, community, and church activities.⁵² The caretaker was the respondent to all questionnaires, except for the Child Health and Illness Profile–Adolescent Edition, which was administered to the youth. For continuous variables, we calculated the means across years and used these averages for analyses. Multiple imputation was used for missing values on the risk and protective factors.⁵³

Study outcomes are behavior problems at ages 5, 7, 9, 11, 13, and 15 years measured by using the Child Behavior Checklist (CBCL).⁵⁴ A trained research interviewer administered the CBCL verbally to all caretakers to ensure uniform administration across sites.

We derived the raw scores for the CBCL internalizing, externalizing, total behavior, and attention scales.⁵⁵

Statistical Analysis

Risk and protective factors were compared across the exposure groups by using analysis of variance for continuous variables and χ^2 tests for categorical variables. We conducted latent growth curve (LGC) modeling by using the Mplus⁵⁶ software to estimate trajectories of CBCL scores over time and examine differences in trajectories according to prenatal drug exposure and risk and protective factors while accounting for clustering of children by site. The risk and protective factors for the final models were selected by using a backward stepwise approach, retaining all factors with $P < .10$ on the intercept and/or slope, controlling for drug exposure. Factors were included in the final models if they remained in the stepwise models for any of the CBCL scores. The risk and protective factor indexes represented the number of the significant risks or protective factors, with a point assigned to each factor with a yes response, or when the average scores or ratings were at the 75th percentile or higher.

In addition to examining the individual factors and the index scores as predictors of trajectories of behavior problems, we also examined the combination of levels of risks and protective indexes to indicate the balance between risks and protective factors. A median split was used to classify risk and protective indexes as high versus low. Low-risk index refers to a cumulative risk index <3 ; a score ≥ 3 indicates high-risk index. Low and high protective indexes represent cumulative scores <2 and ≥ 2 , respectively.

RESULTS

A total of 1388 children were enrolled; 1022 (73.6%) had the CBCL administered

at at least 1 visit and had known levels of PCE. Compared with the 366 (26.4%) children excluded from analysis, those included had higher birth weight ($P = .048$), were more likely to be discharged from the hospital with their mother ($P < .001$), had mothers of younger age ($P = .036$) who were more likely to be black ($P < .001$), and had higher levels of maternal education ($P = .002$). The proportions of high, some, and no PCE did not differ between subjects included versus not included in the analysis.

Table 2 shows mean scores of internalizing, externalizing, total, and attention problems for each year according to the 4 exposure categories. The table also includes proportions or means of other prenatal exposures. Of mothers in the high PCE/OD group, 97% used another substance in addition to cocaine. Risk and protective factors were also compared among the exposure groups. Children with high PCE/OD had significantly greater externalizing and total problem scores than those with PCE-/OD- ($P < .05$) after controlling for risk and protective factors (Table 3). Neither some PCE/OD nor PCE-/OD+ predicted the intercept or slope of any of the behavior problems. Male gender was associated with significantly more externalizing, total, and attention scores at 5 years (intercepts); in addition, male children had significantly lower slopes over time for externalizing and internalizing behaviors. Low verbal IQ was linked to higher initial scores on externalizing, total, and attention problems. Continuing caretaker use of tobacco or alcohol predicted externalizing and total behavior problems. Caretaker psychopathology had significant association with all outcomes, and depression predicted internalizing and total problems. Child abuse was a predictor of total and attention problems at 5 years (intercepts) and was also associated with increasing externaliz-

ing and total problem scores over time (slopes).

High resilience predicted lower scores on all outcomes. Having many friends was associated with lower internalizing and attention problem scores and a decrease in scores at later ages for internalizing ($B [SE] = -0.19 [0.090]$, $P = .042$) and total problems ($B [SE] = -0.81 [0.32]$, $P = .012$). Availability of family resources was significantly associated with lower scores on all behavior outcomes except for externalizing problems. Caretaker involvement was significantly associated with decreases on all behavior scores over time.

When the cumulative risk and protective indexes for each subject replaced the individual factors in the LGC model (Table 4, model 2), high PCE/OD remained a significant predictor for externalizing problems. Some PCE/OD did not predict behavior outcomes. PCE-/OD+ was associated only with increasing internalizing behavior scores (slope) with increasing age. The risk index was a significant predictor of all behavior problems but did not predict significant changes in scores over time. The protective index predicted lower scores in all problems and a significant decrease in scores over time (slopes) for internalizing, total, and attention problems. For risk index, the coefficient (SE) for the intercept was 2.14 (0.20) ($P < .001$) for externalizing problems; for the protective index, the coefficient (SE) for the intercept was $-0.88 (0.24)$ ($P < .001$). Therefore, for externalizing problems, an increase in number of risk factors by 1 would be associated with 2.14-point increase in externalizing scores, whereas an increase of 1 in the number of protective factors would be associated with a 0.88-point reduction in externalizing scores.

With the balance between risk and protective indexes in the final LGC models (Table 4, model 3), all drug-exposed groups predicted externalizing behav-

ior, with the highest coefficient in high PCE/OD. Scores declined with age, but slopes did not differ from PCE-/OD-. High PCE/OD also predicted total problems. All drug exposure groups were associated with attention problems (intercepts); slopes were no different from PCE-/OD-.

The balance between risk and protective indexes was significantly associated with all behavior outcomes. A high-risk index in the presence of low protective index added to the already significant effects of drug exposure. Conversely, a high protective index in the presence of a high-risk index mitigated the predicted associated increased behavior scores from drug exposure. Among children with low-risk indexes, those who also had low protective indexes experienced smaller declines (slopes) in behavior problems over time compared with those with high protective indexes for internalizing ($B [SE] = 0.29 [0.10]$, $P = .004$) and total scores ($B [SE] = 1.00 [0.36]$, $P = .005$). In addition, although not statistically significant, similar trends were found for externalizing ($B [SE] = 0.27 [0.15]$, $P = .062$) and attention ($B [SE] = 0.12 [0.07]$, $P = .065$) problems (Table 4, model 3). Furthermore, when compared with children with low risk and high protective index scores, children with high risk and low protective index scores had smaller declines in total problem scores ($B [SE] = 1.25 [0.47]$, $P = .008$) and attention problem scores ($B [SE] = 0.23 [0.09]$, $P = .008$).

To illustrate the influence of risk and protective indexes on behavior problems, Fig 1 presents the LGCs of CBCL total problem scores over time according to levels of risk and protective indexes separately in the 4 exposure groups. In the high PCE/OD, the high risk-low protective group had significantly higher total problem scores at 5 years (intercept) than the other groups ($P < .05$). The groups with low

TABLE 2 Four Categories of Prenatal Drug Exposure by Specific Drug Exposure, CBCL Scores, and Risk and Protective Factors

Variable	High PCE/OD (n = 115)	Some PCE/OD (n = 235)	PCE-/OD+ (n = 417)	PCE-/OD- (n = 255)
Specific prenatal drug exposure				
Cocaine	115 (100)	235 (100)	0 (0)	0 (0)
Opiate	15 (13)	20 (9)	42 (10)	0 (0)
Marijuana	64 (56)	84 (36)	68 (16)	0 (0)
Alcohol	87 (76)	187 (80)	329 (79)	0 (0)
Tobacco	99 (86)	200 (85)	205 (49)	0 (0)
Marijuana	0.20 ± 0.50	0.11 ± 0.35	0.07 ± 0.32	—
Alcohol	0.81 ± 1.64	0.61 ± 1.17	0.16 ± 0.56	—
Tobacco	12.63 ± 11.93	10.55 ± 10.67	5.30 ± 8.75	—
CBCL Scores				
Externalizing				
5 y ^{a-d}	16.01 ± 9.71	15.10 ± 9.71	13.76 ± 8.50	10.96 ± 7.72
7 y ^{a-d}	15.83 ± 10.34	13.64 ± 9.24	12.98 ± 8.66	9.68 ± 7.29
9 y ^{a-d,f}	14.14 ± 10.52	11.81 ± 8.75	11.92 ± 9.20	8.39 ± 7.95
11 y ^{a-d,f}	12.42 ± 10.07	9.68 ± 7.76	10.10 ± 8.96	7.51 ± 7.91
13 y ^{a-c}	11.27 ± 8.55	9.70 ± 8.30	10.14 ± 8.86	7.28 ± 7.21
15 y ^{a-d,f}	12.60 ± 11.58	9.93 ± 9.16	10.36 ± 9.20	6.73 ± 8.01
Internalizing				
5 y ^{a-c}	6.69 ± 5.49	6.54 ± 5.59	5.86 ± 4.90	4.65 ± 4.48
7 y ^{a,c}	7.99 ± 6.65	6.64 ± 5.74	6.93 ± 5.65	5.64 ± 5.88
9 y ^{a-c}	7.30 ± 7.20	6.14 ± 5.52	6.68 ± 5.96	4.56 ± 5.45
11 y ^{a-c}	7.55 ± 7.04	6.15 ± 5.27	6.76 ± 5.80	4.79 ± 4.96
13 y ^{a-c}	6.16 ± 5.95	5.90 ± 5.65	6.77 ± 6.40	4.44 ± 4.99
15 y ^{a-c,f}	7.38 ± 8.04	5.67 ± 5.77	6.33 ± 5.66	4.16 ± 4.98
Total problems				
5 y ^{a-c,e}	37.62 ± 21.24	35.32 ± 22.17	32.76 ± 18.70	26.00 ± 17.41
7 y ^{a-d}	38.62 ± 24.83	34.12 ± 22.08	33.39 ± 20.97	26.15 ± 18.87
9 y ^{a-d}	35.43 ± 26.07	29.70 ± 20.22	31.03 ± 22.10	21.88 ± 19.65
11 y ^{a-c}	37.17 ± 27.39	30.23 ± 20.94	32.41 ± 23.81	23.80 ± 20.15
13 y ^{a-c}	32.61 ± 23.45	28.93 ± 21.64	32.12 ± 23.64	22.21 ± 18.52
15 y ^{a-c}	34.84 ± 30.17	27.80 ± 23.04	30.41 ± 23.43	20.23 ± 18.99
Attention				
5 y ^{a-c}	4.24 ± 3.05	4.75 ± 3.85	3.84 ± 3.08	2.86 ± 2.59
7 y ^{a-c}	5.49 ± 4.05	5.14 ± 4.26	4.51 ± 3.69	3.42 ± 3.40
9 y ^{a-c,f}	5.62 ± 4.41	4.73 ± 3.70	4.60 ± 3.97	3.61 ± 3.46
11 y ^{a-c,f}	5.64 ± 4.13	4.98 ± 3.80	5.25 ± 4.04	3.83 ± 3.77
13 y ^{a-c}	5.25 ± 4.23	4.97 ± 3.98	5.07 ± 4.00	3.60 ± 3.48
15 y ^{a-c,f}	5.32 ± 4.60	4.53 ± 3.99	4.62 ± 3.98	3.24 ± 3.30
Risk factors				
Male	61 (53)	123 (52)	220 (53)	139 (55)
Head circumference at birth ^{a,c,e}	32.46 ± 2.77	31.92 ± 2.86	32.58 ± 2.98	31.69 ± 3.38
BMI	19.70 ± 4.38	19.10 ± 3.64	19.14 ± 3.58	19.04 ± 3.84
Postnatal tobacco exposure ^{a-e}	101 (88)	215 (91)	282 (68)	57 (22)
Postnatal alcohol exposure ^{a-d}	95 (83)	210 (89)	380 (91)	161 (63)
Postnatal marijuana exposure ^{a-c,e}	41 (36)	102 (43)	126 (30)	14 (5)
Verbal IQ ^{b,e}	87.02 ± 13.21	84.96 ± 11.78	90.02 ± 15.19	88.85 ± 14.72
Full IQ ^{a,e}	85.07 ± 12.06	83.55 ± 10.43	87.86 ± 13.59	87.54 ± 13.44
Child abuse ^b	11 (10)	24 (10)	33 (8)	13 (5)
Caretaker abuse ^{a-c}	35 (30)	70 (30)	96 (23)	28 (11)
Caretaker depression (BDI) ^c	7.63 ± 5.60	7.34 ± 5.36	7.46 ± 5.39	6.42 ± 5.53
Caretaker psychopathology (BSI) ^{a-c}	0.58 (0.46)	0.55 (0.46)	0.54 (0.42)	0.42 (0.40)
Community violence ^{a-e}	5.75 ± 4.00	5.48 ± 3.62	4.69 ± 3.79	3.32 ± 3.22
Protective factors				
Secure attachment	65 (71)	106 (67)	230 (71)	148 (74)
Resilience	22.17 ± 3.07	21.90 ± 3.47	22.42 ± 3.50	22.30 ± 3.64
Home environment ^{b,c}	37.33 ± 5.68	36.05 ± 5.76	36.24 ± 6.49	38.23 ± 6.29
Caretaker involvement ^{a,e}	3.87 ± 0.52	3.80 ± 0.51	3.88 ± 0.50	3.96 ± 0.50
Caregiver supervision	4.48 ± 0.47	4.43 ± 0.51	4.45 ± 0.51	4.46 ± 0.52
SES ^{a-e}	3.70 ± 0.68	3.72 ± 0.66	3.50 ± 0.84	3.33 ± 0.81
Family support scale ^f	3.20 ± 0.68	2.99 ± 0.64	3.07 ± 0.65	3.06 ± 0.69
Family resources scale ^b	122.99 ± 16.89	120.72 ± 15.73	122.87 ± 15.75	125.25 ± 16.32
Neighborhood environment ^{a,b}	3.63 ± 0.84	3.67 ± 0.82	3.78 ± 0.83	3.91 ± 0.79

TABLE 2 Continued

Variable	High PCE/OD (<i>n</i> = 115)	Some PCE/OD (<i>n</i> = 235)	PCE-/OD+ (<i>n</i> = 417)	PCE-/OD- (<i>n</i> = 255)
No. of friends ^a	3.49 ± 0.86	3.38 ± 0.75	3.55 ± 0.82	3.52 ± 0.83
No. of activities	5.05 ± 0.61	5.08 ± 0.62	5.03 ± 0.68	5.08 ± 0.64

Data are presented as *n* (%) or mean ± SD. BDI, Beck Depression Inventory; BSI, Brief Symptom Inventory; SEC, socioeconomic.

^a High PCE/OD versus PCE-/OD- (*P* < .05).

^b Some PCE/OD versus PCE-/OD- (*P* < .05).

^c PCE-/OD+ versus PCE-/OD- (*P* < .05).

^d High PCE/OD versus PCE-/OD+ (*P* < .05).

^e Some PCE/OD versus PCE-/OD+ (*P* < .05).

^f High PCE/OD versus some PCE/OD (*P* < .05).

protective scores generally had flatter curves than those with high protective scores, which seemed to decline over time. Although the differences in slopes between these groups were not significant when compared individually, there was a significant difference in slopes when comparing the 2 low protective groups with the 2 high protective groups ($t[112] = -2.16$, $P = .033$), supporting this general trend based on level of protective influences. Among youths with some PCE/OD, 3 of the 4 groups differed by initial scores at 5 years ($P < .05$) and had similar slopes over time. However, although the remaining high risk-high protective group had scores at 5 years similar to

the high risk-low protective group, they experienced significantly greater declines in problem behaviors over time ($P = .039$). Similar patterns of the influence of protective factors were observed among the 2 groups without PCE (Fig 1). The groups with high protective index scores had significantly different slopes than those with low protective index scores; they declined over time while the low protective groups generally remained flat.

DISCUSSION

After consideration of the balance between risk and protective indexes, high PCE/OD had continued effects on externalizing, total, and attention behav-

ior problems through adolescence. The effects of high PCE/OD on externalizing and total problems were greater than those from other categories of exposure. To our knowledge, this is the first study to explore the effects of PCE as a polydrug problem while considering the balance between cumulative risk and protective factors.

Most studies highlighted the associated risks for adverse outcomes of children with PCE.^{3,5,7,11} PCE is only 1 of many individual-level factors and represents in utero programming resulting in fetal adaptation with long-lasting consequences. Moreover, PCE signals multiple risks in a child's environment. A large number of children with prenatal

TABLE 3 LGC Models of CBCL Scores According to Individual Risk and Protective Factors (Model 1)

Variable	Externalizing		Internalizing		Total		Attention	
	Intercept (B)	Slope (B)	Intercept (B)	Slope (B)	Intercept (B)	Slope (B)	Intercept (B)	Slope (B)
Prenatal drug exposure								
High PCE/OD	2.79*	-0.15	0.83	0.02	5.66*	-0.06	0.75	0.06
Some PCE/OD	0.83	-0.32	0.13	-0.15	1.57	-0.76	0.71	-0.15
PCE-/OD+	1.14	-0.08	0.45	0.10	2.87	0.21	0.51	0.05
PCE-/OD-	REF	REF	REF	REF	REF	REF	REF	REF
Risk factors								
Male	1.64**	-0.27*	0.53	-0.24**	2.78*	-0.45	0.65**	0.08
Low verbal IQ	1.71**	-0.23	-0.18	0.02	3.77*	-0.32	1.01***	0.05
Caretaker depression (BDI)	1.26	-0.04	1.29*	0.05	3.87*	-0.04	0.29	-0.05
Caretaker psychopathology (BSI)	4.11***	-0.21	3.16***	-0.11	11.35***	-0.10	1.41***	0.05
Child abuse	2.07	0.67*	0.66	0.23	4.84*	1.52*	1.01*	0.19
Postnatal tobacco exposure	1.71**	0.15	0.53	0.20	3.32*	0.59	0.49	0.04
Postnatal alcohol exposure	1.53*	-0.01	0.60	-0.06	3.28*	-0.11	0.22	0.00
Protective factors								
Resilience	-1.56*	0.23	-0.96*	0.02	-4.52**	0.48	-0.71**	0.09
Caretaker involvement	-0.34	-0.49**	0.30	-0.35**	0.91	-1.43***	0.36	-0.27***
Family resources	-0.97	0.12	-0.69*	0.06	-2.84*	0.18	-0.51*	-0.01
No. of friends	-0.58	-0.20	-0.67*	-0.19*	-2.33	-0.81*	-0.58*	-0.07

In model 1 (postnatal drug use variables and child abuse): yes versus no, and all else ≥ 75 th percentile versus <75th percentile. BDI, Beck Depression Inventory; BSI, Brief Symptom Inventory; REF, reference category.

* $P < .05$;

** $P < .01$;

*** $P < .001$.

TABLE 4 LGC Models of CBCL Scores According to Cumulative Risk and Protective Indexes (Models 2 and 3)

Variable	Externalizing		Internalizing		Total		Attention	
	Intercept (B)	Slope (B)	Intercept (B)	Slope (B)	Intercept (B)	Slope (B)	Intercept (B)	Slope (B)
Model 2								
Prenatal drug exposure								
High PCE/OD	2.52*	0.02	0.41	0.19	4.45	0.40	0.51	0.06
Some PCE/OD	0.53	−0.14	−0.38	0.02	0.16	−0.31	0.43	−0.13
PCE−/OD+	0.96	0.05	0.17	0.20*	1.90	0.53	0.23	0.06
PCE−/OD−	REF	REF	REF	REF	REF	REF	REF	REF
Cumulative risk index	2.14***	−0.08	1.20***	−0.03	5.28***	−0.03	0.76***	0.03
Cumulative protective index	−0.88***	−0.10	−0.55**	−0.13**	−2.34***	−0.43**	−0.38***	−0.06*
Model 3								
Prenatal drug exposure								
High PCE/OD	3.69***	−0.06	1.09	0.16	7.33**	0.29	0.91*	0.08
Some PCE/OD	1.71*	−0.23	0.30	−0.01	3.10	−0.41	0.85**	−0.12
PCE−/OD+	1.92**	−0.01	0.72	0.18	4.27**	0.45	0.56*	0.07
PCE−/OD−	REF	REF	REF	REF	REF	REF	REF	REF
Risk/protective indices								
High risk, low protective	7.24***	0.18	4.22***	0.25	18.29***	1.25**	2.73***	0.23**
High risk, high protective	5.54***	−0.15	2.77**	−0.05	13.92***	−0.04	2.17***	0.07
Low risk, low protective	1.92**	0.27	1.08**	0.29**	5.25***	1.00**	0.90***	0.12
Low risk, high protective	REF	REF	REF	REF	REF	REF	REF	REF

REF, reference category.

* $P < .05$;** $P < .01$;*** $P < .001$.

drug exposure grow up in homes and communities with violence, with a caretaker who continues to use drugs and has comorbidities or psychological distress associated with her ongoing drug use, low socioeconomic status, and lack of social support.^{29,57–59} As child development progresses, the environment expands, and adverse multiple higher-level family and community factors add to the risk from PCE, exposing a child to an accumulation of risks for later psychopathology.⁶⁰

Nonetheless, not all children or adolescents have behavioral alterations after prenatal drug exposure. Resilience, an individual characteristic, serves as a protective trait in adverse conditions. Investigators have also suggested that resilience can be conceptualized as a process.³² It changes within and across time, and adaptation results from the interaction of risks and protective factors. Specifically, the protective factors at multilevels can enhance the individual's capacity to respond or adapt to adverse conditions.^{32,61}

From the National Youth Survey of Adolescents, multilevel factors predicted or mitigated problem behaviors.³¹ Youth who spent longer time with deviant friends and less time with family had higher levels of problem behaviors over time while those spending more time with family perceived greater family support and exhibited fewer problem behaviors. Also, higher levels of family involvement and parental monitoring predicted a lesser likelihood of problem behaviors.^{30,62} Our findings support the mitigating influence of protective factors at individual, family, and societal levels on youth behavior problems. Therefore, targets for interventions will need to consider resources at multiple levels.³² Our study did have some limitations. Our classification of prenatal exposures does not allow for determination of specific effects of cocaine or each of the OD of exposure. However, our pragmatic approach as to exposure categories, enabled us to compare PCE together with OD from drug use with no cocaine. The fact that we found a greater effect

from high PCE than some PCE suggests a dose-response relationship; establishing causality requires further studies. Also, we did not examine mediation models to determine if PCE may have affected protective factors and thus altered behavior outcomes. We used behavior measures from the caretakers' reports, but school behavior problems may differ from those observed at home. Still, a significant, although modest, relationship exists between caretaker and teacher report of childhood and preadolescent behavior.^{7,63} The CBCL only provides broadband measures without the details from direct observation.

Generalizability of our results may be limited to subjects recruited from urban, high-poverty neighborhoods, but this population is at risk for disparities in physical and mental health, an important factor in designing intervention. Those lost to follow-up may have moved to a higher-risk environment, and our findings are underestimates of effects of risk factors. Classifying levels of PCE by self-report

FIGURE 1

LGC trajectories of CBCL total problems according to prenatal drug exposure and risk and protective factors.

may have underestimated the effects of PCE and OD. In addition, some subjects had opiate exposure, which may overestimate PCE effects. However, the proportion with opiate exposure did not differ among the drug-exposed categories. Finally, our study did not address the influence of heredity, genetics, and genes-environment interactions on behavior outcomes.^{64–66}

CONCLUSIONS

Our findings are pertinent in the care of substance-using women and their children, regardless of whether their choices include cocaine or OD. Prenatal drug exposure is only 1 of many risks for later behavior problems, but exposure does not necessarily portend dismal

outcomes. Clinical practice and public health policies should address drug use prevention, risk reduction (eg, violence prevention), and interventions to enhance protective factors at multiple levels (eg, parenting and foster care training, programs addressing child's friendship skills, interpersonal problem-solving skills),⁶⁷ thereby strengthening the child's resilience in coping with adversity.

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