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Level of Prenatal Cocaine Exposure and Scores on the Bayley Scales of Infant Development: Modifying Effects of Caregiver, Early Intervention, and Birth Weight

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Abstract

Objectives—The objectives of this study were 1) to assess whether there is an independent association between the level of prenatal cocaine exposure and infants' developmental test scores after control of potential confounding variables; and 2) if such an association exists, to determine which biological and social variables, individually and in interaction with each other, may modify it.

Methods—In a prospective, longitudinal study of 203 urban term infants, 3 cocaine exposure groups were defined by maternal report and infant meconium assay: unexposed, heavier cocaine exposure (> 75th percentile self-reported days of use or meconium benzoylecognine concentration), or lighter cocaine exposure (all others). Examiners, masked to exposure history, tested infants at 6, 12, and 24 months of age with the Bayley Scales of Infant Development.

Results—The final mixed linear regression model included as fixed covariates level of prenatal exposure to cocaine, alcohol, and cigarettes; prenatal marijuana exposure; gestational age and birth weight z score for gestational age; and gender. Age at test, caregiver at time of each test (biological mother, kinship caregiver, unrelated foster caregiver), and any previous child-focused early intervention were included as time-dependent covariates. There were no significant adverse main effects of level of cocaine exposure on Mental Development Index (MDI), Psychomotor Development Index (PDI), or Infant Behavior Record. Child-focused early intervention interacted with level of cocaine exposure such that heavily exposed children who received such intervention showed higher adjusted mean MDI scores than all other groups. Although the sample was born at or near term, there was also a significant interaction of cocaine exposure and gestational age on MDI scores, with those in the heavier exposure group born at slightly lower gestational age having higher mean MDI scores compared with other children born at that gestational age.

There was also a significant interaction on MDI between child's age and caregiver. At 6 months, the adjusted MDI of children living with a kinship caregiver was 15.5 points lower than that of children living with their biological mother, but this effect was diminished and was no longer significant at 24 months (difference in means: 4.3 points). The adjusted mean MDI of children in unrelated foster care at 6 months was 8.2 points lower than children of biological mothers, whereas it was 7.3 points higher at 24 months.

Early intervention attenuated the age-related decline in PDI scores for all groups. Birth weight < 10th percentile was associated with lower PDI scores for children with heavier cocaine exposure and with lower MDI scores for all groups.

Conclusions—Heavier prenatal cocaine exposure is not an independent risk factor for depressed scores on the Bayley Scales of Infant Development up to 24 months of age when term infants are compared with lighter exposed or unexposed infants of the same demographic background. Cocaine-exposed infants with birth weight below the 10th percentile for gestational age and gender and those placed with kinship caregivers are at increased risk for less optimal developmental outcomes. Pediatric clinicians should refer cocaine-exposed children to the child-focused developmental interventions available for all children at developmental risk.

Keywords

cocaine; pregnancy; meconium; child development; early intervention; kinship care; foster care

At the beginning of the cocaine epidemic, many predicted that children exposed to cocaine in utero would show lasting developmental impairments. However, peer-reviewed research does not find striking or consistent effects of prenatal cocaine exposure on developmental test scores in the first 2 years of life. Of the 11 studies using masked examiners to evaluate the impact of prenatal cocaine exposure on scores on the Bayley Scales of Infant Development (BSID),^{1,2} 6 found no statistically significant effect,^{3–8} including 1 study that classified infants according to mothers' report of level of prenatal exposure.⁷ Among the 5 studies that did find adverse effects of prenatal cocaine exposure, effects differ by age of assessment and whether exposure to tobacco, alcohol, and marijuana, and other potential confounds were included in the analysis. In a sample of infants whose mothers entered drug treatment during pregnancy, the mean BSID Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) scores of infants whose mothers used cocaine/alcohol/marijuana were lower at 6 months than infants whose mothers did not use these drugs, but identical to those of mothers who had used alcohol/marijuana without cocaine. These results suggest that there is no incremental detrimental impact of cocaine use on development quotients beyond that imposed by the concurrent use of alcohol/marijuana.⁹ No deleterious cocaine effects were detected in this sample on BSID scores at other assessment ages up to 24 months.⁹ Other investigators found a bivariate association of lower PDI scores at 3 months with prenatal cocaine exposure, but not after statistical control for potential confounds.¹⁰ In a sample confined to very low birth weight infants tested at ~ 16 months' corrected age, a negative association with prenatal cocaine exposure was found with MDI and PDI, but in utero exposure to other psychoactive substances was not analytically controlled.¹¹ A study that used the recently revised BSID II² found no main effects of mothers' reported level of prenatal cocaine exposure on MDI or PDI at 8 or 18 months.¹² In posthoc comparisons, children whose mothers reported higher levels of prenatal cocaine use (2 or more days per week) were found to have significantly lower MDI scores at 18 months than those with no exposure.¹² For infants who were unexposed or lightly exposed, higher environmental risk was also associated with a greater decline in MDI scores from 8 to 18 months.¹² Singer et al¹³ found in a large sample a statistically significant decrement in BSID II MDI scores associated with prenatal cocaine exposure, with an increased risk of developmental delay among the exposed. This study contained a substantial number of very low birth weight infants who are excluded from other samples and did not measure whether subjects received developmental intervention.

When adaptive behavior during the testing situation was measured by the Infant Behavior Record (IBR) of the BSID, 2 investigators found cocaine-exposed infants more listless than unexposed infants in bivariate analyses, but not after covariate control.^{3,11}

Contextual factors may partially account for these discrepancies.¹⁴ Prenatal cocaine exposure may exert differing impacts on later developmental outcomes depending on the interaction of exposure with other biological and social factors. Discrepant findings are also susceptible to multiple possible methodologic explanations, including differences in study design, varying patterns of sample attrition, misclassification of exposed infants as unexposed because of inaccurate maternal report, and failure to address potential dose effects.¹⁵ If exposed infants are misclassified as unexposed, between-group differences may be missed. If lightly and heavily exposed infants are aggregated into a single category, cocaine effects that may occur only at higher or lower levels of prenatal exposure may be obscured.⁷

Testing meconium for drug metabolites presents a method of assessing prenatal cocaine exposure that enhances accurate identification of newborns exposed to cocaine prenatally, detecting more exposed infants than mothers' report or peripartum urine assays from mothers or infants.^{16–19} Although not a precise reflection of the total grams of cocaine used by a mother during pregnancy or the gestational timing of use, the concentration of cocaine metabolites in meconium allows newborns to be rank ordered by their relative level of cocaine exposure. This rank order correlates with newborns' birth weight, behavior, and risk of subependymal hemorrhage.^{20–23}

The first goal of this analysis was to assess whether, after control of potential confounding variables, there is an independent association between the level of prenatal cocaine exposure (assessed by mothers' self-report and/or assay of infants' meconium) and infants' scores on the BSID at 6, 12, and 24 months of age. The second goal was to determine which biological and social variables, individually and in interaction with each other, may moderate such an association if one is found.

METHODS

Sample Selection Criteria

The Human Studies Committees of Boston City Hospital (now Boston Medical Center) and the Boston University School of Medicine approved this study. All participants gave informed consent, including the risk of incidental detection and reporting of child maltreatment during study assessments. A writ of confidentiality was obtained from the federal government to protect participants from having research data subpoenaed. The sample was recruited by trained interviewer/recruiters who screened maternity and nursery records 7 days a week on the postpartum floor of Boston City Hospital from October 1990 to March 1993. Unexposed dyads comparable to cocaine-exposed mother-infant dyads in ethnicity (African American/African Caribbean vs other) were preferentially approached for recruitment soon after delivery. All mother-infant dyads met the following criteria based on review of mother and infant medical records and confirmed by interviews, biological markers, and infant physical examinations obtained by study personnel: 1) Infant gestational age greater than or equal to 36 weeks; 2) No requirement for neonatal intensive care; 3) No obvious major congenital malformations; 4) No diagnosis of fetal alcohol syndrome in the neonatal record; 5) No history of human immunodeficiency virus seropositivity noted in the mother's or infant's medical record; 6) Mother's ability to communicate fluently in English; 7) No indication by neonatal or maternal urine toxic screen or history in medical record of mother's use during pregnancy of illegal opiates, methadone, amphetamines, phencyclidine, barbiturates, or hallucinogens; and 8) Mother aged 18 years or older. These criteria were established to exclude infants with known major risk factors that might confound or obscure the effects, if any, of in utero cocaine exposure. The sample was restricted at recruitment to mothers with English fluency, because many of the neuropsychological measures planned for this cohort at preschool and older ages are not standardized for populations whose first language is not English. Additional details about sample characteristics and recruitment are reported elsewhere.^{21,23}

Method of Exposure Classification

Mothers participating in the study were identified as either heavier, lighter, or nonusers of cocaine by interview and by biological markers obtained by clinicians and study personnel. At intake on the postpartum floor, research assistants using the Addiction Severity Index²⁴ supplemented by study-specific questions interviewed the mothers about pregnancy and lifetime use of cigarettes, alcohol, and illicit drugs. We sought to collect meconium specimens from all enrolled infants to be analyzed by radioimmunoassay for benzoylecognine (a cocaine metabolite), opiates, amphetamines, benzodiazepines, and cannabinoids. The radioimmunoassay used was a modification of the method of Ostrea et al,^{17,19} published in detail elsewhere.

During the period of study recruitment at Boston City Hospital, urine testing for metabolites of illicit drugs was performed for clinical indications at the discretion of health care personnel, but was not universal. We documented the results (when available in the medical record) of the urine drug enzyme multiplied immunoassay technique assays obtained for clinical purposes during prenatal care or labor and delivery from mother or from the infant after birth. Although cases were targeted for recruitment on the basis of self-report or positive clinical urine assays, comparison mothers were drawn from the maternity population as a whole, most of whom did not have urine assays performed for drug metabolites for clinical purposes. Therefore, after recruitment and informed consent, we collected additional urine samples from all study mothers for analysis for benzoylecognine, opiates, amphetamines, benzodiazepines, and cannabinoids by radioimmunoassay using commercial kits (Abuscreen RIA, Roche Diagnostics Systems, Inc., Montclair, NJ).

Subject Exposure Classification

All mother-infant dyads had at least 1 biological marker, either urine from mother or infant or meconium, which confirmed their exposure or lack of exposure to cocaine during pregnancy. In this sample, the mean days of self-reported cocaine use during pregnancy was 20.6 days, with a range from 0 to 264. The mean meconium concentration of benzoylecognine/g was 1143 ng with a range from 0 ng to 17 950 ng per g. Before data were analyzed, a composite measure of “heavier” use was a priori defined as the top quartile of meconium concentration for cocaine metabolites (> 3314 ng of benzoylecognine/g meconium) and/or top quartile days of self-reported use (> 61 days) during the entire pregnancy. All other use was classified as “lighter.”²⁴ This ordinal classification scheme is comparable to that used by other investigators,^{7,12,25} where use of cocaine more than twice a week during pregnancy is considered “heavier” use.

Pragmatic as well as scientific considerations influenced this definition of exposure level. Because women are more likely to underreport rather than overreport illicit substance use during pregnancy,^{17,26} we decided a priori that women reporting days of use in the top quartile should be considered heavier users, even if the benzoylecognine levels in meconium were not in the top quartile. Not all infants exposed to cocaine in utero have positive meconium assays.¹⁸ Moreover, we were not able to obtain meconium samples from 14% of study infants, whose exposure status was confirmed by maternal or infant urine assay. Therefore, whichever indicator (self-report or meconium assay) demonstrated higher exposure was used to define exposure category.

Outcome and Control Variables

BSID—The raw scores of the BSID generate the MDI and a PDI, both standardized to have a mean of 100 and a standard deviation of 16. These standard scores are supplemented by the IBR, a group of descriptive rating scales of infants' behavior during testing, including interpersonal and affective domains, motivational variables, and interest in specific modes of

sensory experience. For the analyses in this study, 3 summary scores (task orientation, extroversion, activity), were generated from the IBR rating according to the method of Matheny.²⁷

In 1993, the BSID was renormed and standardized as the BSID II.² Because this longitudinal study began before the availability of the new version, we continued to use the original version of the BSID for all assessments to facilitate uniform interpretation.

Ongoing interrater reliability checks on the scoring of the BSID (agreement of pass/fail on test items within the MDI and PDI) averaged above 90% (range: 81%–100%) agreement. At all ages the BSID was performed by examiners masked to the children's exposure status.

Control Variables—Potential control variables were selected on theoretical grounds at the start of the study and included infant anthropometric characteristics and health parameters repeatedly measured from birth to age 2 years. Within 8 to 72 hours of birth (mean: 48 hours), a study pediatrician, trained to reliability and unaware of the infants' cocaine exposure, assessed gestational age according the method of Dubowitz et al²⁸ and measured recumbent length on a Holtain Infantometer (Holtain Ltd, Crymych Pembs, United Kingdom) and head circumference with a plastic-coated tape. The pediatrician also reviewed the infant's medical record for birth weight (measured after delivery by nursery nurses using a Detecto scale [Jericho, NY]) and neonatal medical complications using a list adapted from the work of Hobel.²⁹ Child health data for the first 2 years of life were abstracted in a standard format from caregiver reports and medical records.

At the time of each developmental assessment, trained interviewers unaware of the child's developmental status administered a follow-up version of the Addiction Severity Index to the care-giver, as well as Saranson's (1978) Life Experience Survey,³⁰ Norbeck's (1981) Social Support Questionnaire³¹ and the Center for Epidemiologic Studies Depression Scale.³² The interviewers also elicited information regarding caregivers' exposure to violence using a questionnaire developed for the primary care pediatric clinic at Boston City Hospital.³³ To characterize from the child's perspective the social environment over the first 2 years of life, scores on each instrument were averaged, even if different care-givers responded at different ages. To enhance the accuracy of self-reporting of postpartum use of illegal substances,³⁴ respondents' urine was collected after each interview and assayed by radioimmunoassay for metabolites of cocaine and marijuana. The interviews and urine assays were obtained for research purposes only and were not recorded in the caregiver's or the child's medical record. At each assessment, caregivers reported whether the child had received any child-focused developmental intervention since the previous interview. These included a range of intervention services from professionals and paraprofessionals, with delivery models including formal early intervention programs, home health services, parent-child groups, and/or services from individual clinicians such as occupational, speech, and physical therapists.

In addition to completing interviews at the hospital, caregivers of 84% of the unexposed, 83% of the lightly exposed, and 82% of the heavily exposed children ($P = .64$) permitted at least 1 visit by a research home visitor. These home visitors were masked to the child's exposure status and developmental data, and performed the Home Observation for Measurement of the Environment (HOME)³⁵ and Nursing Child Assessment Teaching Scale (NCATS).³⁶ After each laboratory or home visit, caregivers received store vouchers valued at \$25, and children received an age-appropriate toy.

Statistical Methods

To assess possible confounding, we performed bivariate analyses to compare the groups at each level of cocaine exposure on the control variables using χ^2 tests for categorical variables and 1-factor analysis of variance for measurement variables.

Bivariate analyses were also used to compare the 3 cocaine exposure groups on the BSID MDI and PDI and on the 3 summary scores of the IBR at 6, 12, and 24 months infant age, using 1-factor analysis of variance.

In multivariate analyses, we used mixed linear regression models to analyze repeated observations from each child, which were included in a single analysis for each outcome (MDI, PDI, IBR) by specifying a within-subject correlation structure. This technique maximizes statistical power, allowing the detection of subtle effects in a longitudinal data set with data missing at some points because of subject attrition or noncompliance. These models were also used to allow for time-dependent covariates, such as child's foster placement or participation in early intervention programs, which may differ at each assessment age. In each mixed model, we first determined a main effects-only model (not shown) that included potential confounding variables. We then examined all possible 2-way interactions between the independent variables in the final model. Interactions that were significant at .05 level were retained in the final model. Adjusted means and effects of level of cocaine exposure or other predictors on BSID scores are shown computed from the estimated parameters from these regression models (Tables 1 and 2). *P* values noted in the text and not shown in tables were also based on parameter estimates and their standard errors. For interaction effects, adjusted means and effects were based on contrasts involving 2 or more parameter estimates from the model.

In fitting these models, we used different, plausible working correlation structures and compared their computed values for Akaike's Information Criterion. For each outcome, we selected the working structure that yielded the Akaike's Information Criterion closest to zero.³⁷ We denote results as statistically significant if 2-tailed *P* values were less than .05.

The choice of covariates for the final models presented in this study reflect both theoretical and analytic considerations. Prenatal exposure to cigarettes, marijuana, and alcohol were included as covariates in the final model because in human samples, cocaine use rarely occurs without concomitant use of 1 or more of these substances.¹⁸ In these models, prenatal cigarette use was measured as the average daily number of cigarettes and the prenatal alcohol use measured in average daily volume. Prenatal marijuana use took the form of a binary variable ("yes"/"no") based on positive results of urine assay, meconium assay, or self-report. To address potential multicollinearity among these variables characterizing prenatal substance use, we performed formal collinearity diagnostics by the methods of Belsey, Kuh, and Welsch.³⁸ These diagnostics indicated no presence of multicollinearity that would degrade the estimates obtained from our models.

However, caregivers' postpartum use of alcohol and cigarettes (by self-report), and of marijuana and cocaine (by self-report or urine assay), was so highly correlated with prenatal use that the effects, when prenatal use was excluded from the analysis, were similar to that of prenatal use, and thus could not be included in the same regression model. (Analyses available from author on request.)

Other covariates were retained in the final model if their inclusion altered the unadjusted association between level of cocaine exposure and outcome by > 10%. The variables that were tested included infants' biological characteristics at birth and through the first 2 years of life, and biological mothers' and other caregivers' demographic, medical, and psychosocial

characteristics, summarized in Tables 3–5. Where relevant, we modeled each of these variables as a time-dependent covariate, eg, HOME score at 5, 11, or 23 months.

RESULTS

Sample Retention

We found no significant differences between the 203 children who are the subjects of these analyses and the 49 infants enrolled at birth who did not complete Bayley testing on level of cocaine exposure ($P = .91$) and other baseline variables measured at intake: birth weight ($P = .24$); gender ($P = .35$); gestational age ($P = .12$); maternal age ($P = .79$); maternal education ($P = .57$); ethnicity ($P = .11$); primiparity ($P = .57$); and prenatal alcohol ($P = .22$); cigarette ($P = .44$); and marijuana exposure ($P = .39$) via 2-sample t tests and χ^2 tests.

Sample Characteristics

Table 3 shows sample characteristics for the 3 pre-natal exposure groups. Maternal education did not differ significantly between groups. However, non-users were significantly younger than users and tended to be primiparas. African American/African Caribbean mothers were disproportionately found in the noncocaine-using or heavier cocaine-using groups, whereas Hispanic/white mothers were more likely to be lighter users. Heavier cocaine use was associated with heavier use of tobacco, alcohol, and marijuana during pregnancy. As summarized in Table 3, the infants in the 3 exposure groups did not differ in gender or in rates of depressed Apgar scores (< 7) at 5 minutes. Although the sample was restricted at recruitment to infants born at ≥ 36 weeks, heavier cocaine use was associated with shorter infant gestation and lower birth weight, length, and head circumference z scores adjusted for gender and gestational age (based on norms calculated from the data file compiled by the National Center for Health Statistics for natality in the United States in 1991).³⁹ In the sample retained for BSID assessment, as in the neonatal sample, heavier cocaine exposure was associated with significantly increased risk of sub-ependymal germinal matrix hemorrhage by neonatal ultrasound and a trend toward less optimal state regulation at 3 weeks of age on the Neonatal Behavioral Assessment Scale.^{21,23,40} Despite these differences in medical risk at birth, the 3 groups did not differ in mean z score for weight, length, or head circumference at subsequent measurements (data not shown, available from authors on request), or in rates of anemia, elevated lead levels, or recurrent otitis in the first 2 years of life. Children in the “lighter” cocaine exposure category were more likely than the unexposed to have been hospitalized at least once in the first 2 years of life.

Table 5 also shows that in contrast to medical risks, social risks other than homelessness were associated with level of cocaine exposure. Infants with heavier cocaine exposure experienced the greatest number of changes in caregivers and were the most likely to be placed out of biological mother’s custody and with unrelated foster parents.

Table 5 demonstrates that when scores were averaged over the first 2 years of the child’s life, caregivers in the 3 exposure groups did not differ on depressive symptoms, reported negative life events, exposure to violence, or living with a male partner. However, caregivers of cocaine-exposed children used significantly more cocaine, cigarettes, and alcohol during the first 2 years of the child’s life compared with the caregivers of nonexposed children. Caregivers of infants with heavier cocaine exposure were the most likely to use marijuana in the postpartum period. The caregivers of the children with lighter cocaine exposure perceived the lowest levels of social support. As Table 5 shows, children with heavier cocaine exposure were more likely to receive developmental intervention before their first birthday than those with lighter exposure or no exposure ($P = .08$). The 3 groups did not differ significantly in the receipt of day care in the first 24 months of life. The mothers of the more heavily cocaine-exposed infants

were most likely to receive residential drug treatment. Among the 169 children with at least 1 HOME/NCATS³⁶ assessment, there were no significant differences by level of cocaine exposure for average (shown in Table 5), minimum, or maximum HOME or NCATS scores.

Effect of Cocaine on MDI and PDI in Bivariate Analyses

Table 6 summarizes the bivariate relationship between level of cocaine exposure and MDI and PDI scores at each assessment interval. Numbers assessed at each interval vary. No significant differences were observed across cocaine exposure groups at any assessment age for either MDI or PDI.

Multivariate Analyses

In Tables 1 and 2, we present adjusted means from the final models for MDI and PDI, including the variables that altered cocaine's relationship to these outcomes. The final mixed linear regression model included as fixed covariates, level of prenatal exposure to cocaine, alcohol, and cigarettes, prenatal marijuana exposure, birth weight *z* score, gestational age, and gender. Age at test, caregiver at time of each test (biological mother, kinship caregiver, unrelated foster caregiver), and any previous child-focused early intervention were included in the analysis as time-dependent covariates. Although average psychosocial scores are presented in Table 5, we also tested caregivers' depressive symptoms and life stress as time-dependent covariates. These time-dependent covariates did not achieve statistical significance, nor demonstrate additional confounding or interaction effects and so were excluded from the final model.

Effect of Cocaine on MDI in Multivariate Analyses

Multivariate analysis showed an apparently paradoxical positive effect of level of cocaine exposure on MDI (Table 1). This effect was explained by a significant interaction between cocaine and early developmental intervention ($P = .03$). Among children with no early intervention, there were no significant differences in adjusted MDI by cocaine exposure. There was no significant effect of early intervention within the groups of unexposed and infants with lighter cocaine exposure, but children with heavier exposure who received early intervention had significantly higher adjusted scores than all other groups.

Multivariate analysis showed additional effects of birth weight, age, early developmental intervention, and caregiver on MDI, regardless of cocaine exposure. Infants with birth weight at the 10th percentile for gender and gestation, the conventional cutoff for "small for dates" had lower adjusted MDI scores (by 2.5 points; $P = .02$) than those at the 50th percentile. Although the sample was all born at or near term, there was also a significant interaction of cocaine exposure and gestational age on MDI scores ($P = .006$) with those in the heavier exposure group born at slightly lower gestational age having higher mean MDI scores compared with other children born at that gestational age.

MDI scores declined with age. The extent of the decline varied by type of caregiver. Adjusting for level of prenatal exposure to cocaine and other substances, birth weight *z* score, and gestational age, there was also a significant interaction ($P = .008$) between child's age and caregiver on MDI. For children living with their biological mother or in kinship care, adjusted MDI scores dropped significantly from 6 months to 24 months; for children in unrelated foster care, the decline in scores from 6 to 24 months was not statistically significant.

The caretaker by age interaction reported above can also be interpreted in terms of differences in adjusted mean MDI by caregiver (biological mother, kinship care, and unrelated foster care). Children in kinship care had lower adjusted mean MDI scores than children in the care of their biological mothers at both 6 and 24 months. In contrast, children in unrelated foster care had lower adjusted mean MDI scores at 6 months, but had higher adjusted mean MDI than the

children with their biological mothers at 24 months. At 6 months, the adjusted MDI of children living with a kinship caregiver was 15.5 points lower than that of children living with their biological mother ($P = .0003$), but this effect was diminished and was no longer significant at 24 months (difference in means = 4.3 points; $P = .18$). The adjusted mean MDI of children in unrelated foster care at 6 months was 8.2 points lower than children of biological mothers ($P = .06$), whereas it was 7.3 points higher at 24 months ($P = .11$).

Effect of Cocaine on PDI in Multivariate Analyses

For PDI, multivariate analysis showed no significant main effects of prenatal cocaine exposure. However, a significant interaction between cocaine exposure and birth weight z score ($P = .02$; Table 2) was found. For example, for infants at the tenth percentile in birth weight, more heavily exposed infants had an adjusted mean PDI that was comparable to those observed for the lighter and unexposed groups of infants. For infants with birth weight at the 50th percentile, however, more heavily cocaine-exposed infants had higher adjusted mean PDI scores than unexposed by 7.1 points and more lightly exposed infants by 6.8 points.

Multivariate analysis showed additional effects of age, early developmental intervention, caregiver, and gestational age on PDI, controlling for prenatal exposure to cocaine and other psychoactive substances. There was a significant interaction between age and early developmental intervention ($P = .04$). Intervention attenuated the age-related deterioration in PDI scores. For children not receiving intervention, there was a significant 3.8-point drop in adjusted PDI scores from 6 to 24 months ($P = .01$), whereas for infants receiving intervention there was a 9.6-point increase over the same period ($P = .08$).

A significant interaction between caregiver and early developmental intervention on adjusted PDI ($P = .01$) was found. Children living in kinship care and receiving intervention had adjusted PDI scores 14.7 points lower than those not receiving intervention ($P = .005$). No such significant effect was found for those in biological mothers' or nonkinship care.

Effect of Cocaine on IBR Scores in Bivariate and Multivariate Analyses

In addition to BSID MDI and PDI, we examined summary scores calculated from the IBR as dependent variables. There was no bivariate relationship between the level of cocaine exposure and the child's scores on the extroversion, task orientation, or activity level clusters²⁷ of the IBR at 6, 12, or 24 months. In multivariate analyses that included the same variables that were controlled in the multivariate analyses of the MDI and PDI, no significant cocaine effect was identified. (Analyses not shown, but available from the authors on request.)

Effects of Alcohol, Marijuana, and Cigarettes on MDI and PDI in Multivariate Analyses

No significant independent effects of prenatal alcohol, marijuana, or cigarette use on MDI scores were found. In contrast, the adjusted PDI showed a significant paradoxical relationship with prenatal cigarette exposure ($P = .007$). For example, children whose mothers smoked a pack of cigarettes per day had higher adjusted mean PDI scores by 6.4 points than children of nonsmokers.

DISCUSSION

This study is one of the first to utilize assays of neonatal meconium for cocaine metabolites in addition to mothers' self-report to evaluate whether there is a dose-response relationship of level of prenatal cocaine exposure with scores on the BSID from 6 to 24 months. Although adverse dose effects of prenatal cocaine exposure were observed in the neonatal period in this sample,^{22,24} in bivariate and multivariate analyses, no adverse independent effects of level of cocaine exposure were found on the BSID MDI, PDI, or IBR from 6 to 24 months. However,

we observed a number of important interaction effects of level of cocaine exposure with biological and social factors. Three biological factors— older age at test, gestational age at birth, and lower birth weight *z* score—were associated with less optimal developmental performance. Developmental test scores declined with increasing age at time of testing for both cocaine exposed and unexposed infants, replicating the findings of other longitudinal studies.^{6,9} Lower birth weight was associated with less optimal MDI scores regardless of cocaine exposure and with lower PDI scores for heavily exposed children. Within this sample of term and near-term infants, gestational age had no independent association with test scores, but paradoxically, lower gestational age seemed to have less adverse effect on MDI scores for children with heavy cocaine exposure than for the other exposure groups.

Two social factors, placement and child-focused developmental intervention, influenced the children's developmental test scores in interaction with level of prenatal cocaine exposure and with each other. In this sample, there was no difference in infant perinatal characteristics among cocaine-exposed infants discharged to their biological mothers after birth compared with those discharged to kinship or unrelated foster care. (Data not shown, available by request.) However, at later ages, children in kinship care attained lower scores on the BSID than children who remained with their biological mothers or were placed in unrelated foster care, regardless of early intervention. Our clinical experience suggests that children in kinship care receive intervention only after they have developed more severe impairments than those triggering intervention for children in other groups. Others have noted unrecognized and untreated developmental deficits among school-age children in kinship care.⁴¹ In Massachusetts, as in other parts of the country, kinship caregivers receive less financial support and less monitoring from social service agencies than unrelated foster parents.⁴²

The developmental interventions received by children in this study were those available from publicly funded early intervention and public health nursing programs in Massachusetts⁴³ to any infant at developmental risk, and were not specifically targeted to infants with prenatal drug exposure. The clinicians that provided the interventions were not associated with the research project, so that the details of the services received by each child are not known. Home visiting and early intervention services in Boston vary in intensity, site of delivery (home or center), and in the areas of expertise (eg, speech, education, occupational, physical therapy, nursing) of the intervention staff, depending on the child's neighborhood and the referring preferences of the pediatric health provider.⁴¹ Caregiver participation is encouraged in all programs. Although heterogeneous, these interventions exerted statistically significant protective effects on the cognitive development of heavily cocaine-exposed infants and on the psychomotor development of infants regardless of their cocaine exposure. These findings are consistent with those of randomized studies showing beneficial impact of such interventions for at-risk infants without known cocaine exposure.^{44,45} Moreover, positive results of home visiting interventions for cocaine-exposed infants^{8,46,47} have been reported in uncontrolled, descriptive studies.

Alternate possible explanations are possible for the paradoxical finding that early intervention has the greatest impact on the MDI scores of the infants with the heaviest prenatal cocaine exposure. On the one hand, this finding may only reflect the fact that heavily exposed children received intervention earlier than did unexposed or lightly exposed children (Table 5). We infer that the lower birth weight and less optimal neonatal behavior of infants who were more heavily exposed (Table 4) or clinician awareness of the child's exposure history may have resulted in earlier and more frequent referrals, although their developmental test scores at 6 months did not suggest that obvious developmental delay was an indication for referral.

On the other hand, intriguing preliminary research suggests that perinatal cocaine exposure enhances animals' responsiveness to early environmental manipulations such that beneficial

early experiences exerted protective effects when cocaine-exposed animals experienced later stressors, effects not detected in unexposed comparisons.⁴⁸ Whether heavy prenatal cocaine exposure confers on humans similar “supersensitivity” to positive environmental input merits additional study.

Contrary to expectations, there were no statistically significant interactions between level of prenatal cocaine exposure and prenatal exposure to cigarettes, alcohol, or marijuana on BSID scores. There was a paradoxical main effect of cigarettes. Heavier prenatal exposure to cigarettes was associated with higher PDI scores. An analogous positive effect of prenatal cigarette exposure on pegboard tasks has been described in a Canadian cohort.⁴⁹

These results should be judiciously interpreted in light of the limitations imposed by study design. This study’s site and sample selection criteria limit the generalizability of our findings to similar samples of predominantly African American, urban, term infants who are not acutely ill at birth. Interaction analyses of cocaine effects among subgroups as we have conducted also reduce the effective sample size, and their results may be reliant on the characteristics of the sample. These findings should not be overgeneralized to prematurely born infants or to children who were prenatally exposed to other stimulants or opiates in addition to cocaine. Because the purity and dosage of street drugs vary widely, the actual pharmacologic dose exposure of the lighter and heavier groups in this sample may not be precisely comparable to the dose received by children in other samples who are also classified as “lighter” or “heavier.”^{7,12,25} To maintain this longitudinal sample, all participants, cocaine exposed or not, received pediatric care and intensive outreach from research staff with offers of referrals for caregivers to address diverse problems ranging from need for emergency food to requests for drug treatment. Therefore, the findings may not apply to children whose families have scant contact with health providers. Because the effect of study participation may minimize between-group differences, differences found are likely to be robust.

Lack of adverse cocaine effects on the BSID, a single apical test, as the sole developmental measure, also warrants cautious interpretation. The first edition of the BSID detects effects of prenatal exposure to potential behavioral teratogens other than cocaine, including alcohol,⁵⁰ polychlorinated biphenyls,⁵¹ and lead,⁵² and so might be expected to be sensitive to cocaine effects if such effects are of comparable magnitude. However, others have noted effects of heavier cocaine exposure on language precursors²⁵ and on narrow band measures, such as novelty preference or visual habituation, despite no effects on BSID scores.⁷ We cannot address these domains with our data.

The negative impact of placement with kinship caregivers and the positive impact of early developmental intervention must also be viewed circumspectly, because these factors were not randomly assigned to study subjects. Because of the relatively small number of individuals in each placement/intervention group, we urge particularly cautious interpretation of the significant interaction effects between placement and intervention that we have reported.

Nevertheless, the current study provides some insights to guide pediatric practice. Pediatric clinicians can reassure caregivers and social service agencies that prenatal cocaine exposure is not a potent risk factor for depressed scores on developmental tests up to 24 months when term infants are compared with unexposed infants of the same demographic background. Cocaine-exposed infants with birth weight below the 10th percentile and those placed with kinship caregivers are at increased risk for poorer developmental outcome and warrant particularly close monitoring and support. However, in contrast to birth weight adjusted for gestational age and gender, slightly lower gestational age within a cohort of term infants does not seem to increase risk of adverse outcome after in utero cocaine exposure. This suggests that rate of growth during gestation, rather than absolute duration of gestation within the range

of term or near term, is the more important predictor of outcome after in utero cocaine exposure. Thus, infants who are relatively small for dates (10th percentile or below) at term warrant particularly careful scrutiny. Two protective factors that are environmentally modifiable were observed—participation in child-focused developmental intervention, particularly if such participation began in the first year of life, and placement in unrelated foster care. Pediatric clinicians can play a critical role in assuring that high-risk children, including those who have a history of cocaine exposure, are referred to the developmental services available in their community soon after birth. Our data suggest the widely held belief that prenatally cocaine-exposed children need extraordinary interventions different from those available to other children at risk may not be accurate. Pediatricians can also advocate for measures to decrease caregiver burden, increase resources, and enhance supervision for caregivers providing kinship care to the level of that provided for unrelated foster parents.⁴¹ Additional research will delineate which risk and protective factors influence developmental outcome beyond infancy among children exposed to cocaine prenatally.

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ABBREVIATIONS

BSID	Bayley Scales of Infant Development
MDI	Mental Development Index
PDI	Psychomotor Development Index
IBR	Infant Behavior Record
HOME	Home Observation for Measurement of the Environment
NCATS	Nursing Child Assessment Teaching Scale

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TABLE 1Mixed Linear Model: BSID MDI ($N = 507$ Observations on 203 Children)*

Effect	Effect P Value	Adjusted Mean *	Standard Error
Prenatal cocaine by intervention	.03		
No intervention			
Cocaine unexposed		103.1	1.4
Lighter cocaine		104.8	1.4
Heavier cocaine		106.5	2.3
Intervention			
Cocaine unexposed		99.0	3.8
Lighter cocaine		103.2	3.5
Heavier cocaine		116.5	3.5
Prenatal cocaine by gestational age	.006		
39 weeks' gestational age			
Cocaine unexposed		101.0	1.8
Lighter cocaine		101.1	1.6
Heavier cocaine		110.7	2.5
40 weeks' gestational age			
Cocaine unexposed		102.5	1.3
Lighter cocaine		104.3	1.3
Heavier cocaine		107.8	2.1

* Adjusted means computed from estimated model parameters, adjusting for birth weight z score, prenatal marijuana use (yes/no), natural log of the number of prenatal cigarettes smoked, the natural log of prenatal average daily volume of alcohol, age at assessment, caretaker type at time of assessment, and the interaction of age at assessment with caregiver type.

Note: main effects P values: prenatal cocaine, $P = .004$; intervention, $P = .53$; gestational age, $P = .40$. Full model available from authors on request.

TABLE 2Mixed Linear Model: BSID PDI ($N = 507$ Observations on 203 Children)*

Effect	Effect <i>P</i> Value	Adjusted Mean*	Standard Error
Prenatal cocaine by birth weight <i>z</i> score	.02		
Birth weight <i>z</i> score at 50th percentile ($z = 0$)			
Cocaine unexposed		101.6	5.0
Lighter cocaine		101.9	5.6
Heavier cocaine		108.7	5.9
Birth weight <i>z</i> score at 10th percentile ($z = 1.28$)			
Cocaine unexposed		102.6	4.4
Lighter cocaine		98.8	4.1
Heavier cocaine		101.3	4.2

* Adjusted means computed from estimated model parameters, adjusting for Dubowitz gestational age, prenatal marijuana use (yes/no), natural log of the number of prenatal cigarettes smoked, the natural log of prenatal average daily volume of alcohol, age at assessment, previous history of child-focused intervention as of time of assessment, and caretaker type at time of assessment, the interaction of age at assessment with previous intervention, and the interaction of previous intervention with caretaker type.

Note: Main effects *P* values: prenatal cocaine, $P = .12$; birth weight *z* score, $P = .07$. Full model available from authors on request.

TABLE 3

Prenatal Characteristics of Biological Mother

Prenatal Characteristics of Biological Mother	In Utero Cocaine Exposure			P Value
	Unexposed N = 90	Lighter N = 75	Heavier N = 38	
Ethnicity				
African American/Caribbean	92%	82%	92%	.02
White/Hispanic/Other	8%	18%	8%	
Parity				
Primiparous	44%	29%	34%	.13
Age at delivery (y) *	25.0 (5.3)	27.7 (5.1)	26.8 (3.8)	.002
Maternal education (y) *	11.5 (1.5)	11.4 (1.4)	11.5 (1.0)	.83
Prenatal cigarette smoking				
Nonsmoker	84%	38%	16%	.001
< 1/2 pack cigarettes/d	3%	28%	41%	
1/2-1 pack cigarettes/d	8%	22%	27%	
> 1 pack cigarettes/d	5%	12%	16%	
Average prenatal cigarettes/d during pregnancy *	0.6 (1.8)	3.1 (2.1)	6.4 (1.9)	.0001
Prenatal alcohol and drug use				
Average daily volume of alcohol (ounces of absolute alcohol/d) *	0.02 (.01)	0.17 (0.53)	0.37 (0.87)	.0001
Prenatal marijuana use	9%	33%	42%	.001

* Mean (standard deviation).

TABLE 4
 Infant Perinatal and Postnatal Biologic Risk Factors by Level of Cocaine Exposure

Perinatal and Postnatal Biologic Risk Factors	In Utero Cocaine Exposure			
	Unexposed <i>N</i> = 90	Lighter <i>N</i> = 75	Heavier <i>N</i> = 38	<i>P</i> Value
Perinatal Characteristics				
Dubowitz gestational age (wk) ^{*28}	40.3 (1.2)	39.9 (1.2)	39.9 (1.2)	.06
Birth weight, <i>z</i> score ^{*39}	0.20 (1.1)	−0.43 (0.89)	−0.75 (1.00)	.0001
Birth length, <i>z</i> score ^{*39}	−0.42 (0.93)	−0.94 (0.91)	−1.51 (1.10)	.0001
Birth head circumference, <i>z</i> score ^{*39}	−0.07 (0.97)	−0.44 (1.06)	−0.82 (1.01)	.0005
Subependymal germinal matrix	24%	23%	50%	.005
Hemorrhage				
State regulation at 3 wk	4.6 (1.3)	4.4 (1.1)	3.1 (1.1)	.13
Apgar (5 min) < 7	<i>N</i> = 88 1% <i>N</i> = 82	<i>N</i> = 70 0% <i>N</i> = 65	<i>N</i> = 38 3% <i>N</i> = 38	.44
Infant gender				
Male	56%	49%	47%	.61
Postnatal risk factors				
Any blood Pb Level, > 10 in first 24 mo	27%	18%	22%	.52
Any hemoglobin level, < 11 in first 24 mo	28%	27%	30%	.95
Otitis prone (3 or more otitis events in first 24 mo)	28%	17%	16%	.17
Hospitalized in first 24 mo	14%	28%	13%	.05

* Mean (standard deviation).

TABLE 5
Postnatal Environmental Factors Over First 24 Months of Infant's Life by Infant Cocaine Exposure

Postnatal Environmental Factors	In Utero Cocaine Exposure			
	Unexposed <i>N</i> = 90	Lighter <i>N</i> = 75	Heavier <i>N</i> = 38	<i>P</i> Value
Caretaker average Depressive Symptoms score ^{*†32}	11.3 (6.6)	9.2 (7.0)	8.9 (9.5)	.11
Caretaker average Negative Life Events score ^{*†30}	7.8 (6.2)	6.4 (6.4)	7.0 (11.8)	.51
Caretaker average Social Support score ^{*†31}	68.8 (37.5)	58.7 (40.3)	79.7 (50.1)	.04
Caretaker lived with a male partner	49%	43%	43%	.68
Caretaker exposed to violence	8%	7%	8%	.95
Caretaker positive for cocaine by self-report or assay	11%	40%	56%	.001
Caretaker positive for marijuana by self-report or assay	13%	13%	37%	.01
Average number of cigarettes caretaker smoked [*] per d [†]	<i>N</i> = 84 1.0 (2.0)	<i>N</i> = 55 3.8 (2.4)	<i>N</i> = 27 5.0 (1.6)	.0001
Caretaker average daily volume of alcohol (ounces of absolute alcohol/d) ^{*†}	<i>N</i> = 85 0.15 (.22)	<i>N</i> = 54 0.18 (.27)	<i>N</i> = 27 0.65 (1.12)	.007
Average HOME Inventory score ^{*†35}	37.6 (4.1)	37.5 (5.0)	39.0 (5.3)	.28
Average NCAT score ^{*†36}	<i>N</i> = 81 59.8 (5.0)	<i>N</i> = 60 59.6 (7.2)	<i>N</i> = 31 58.6 (5.5)	.61
Child placement history				
Biological mother only	90%	63%	50%	.001
Any kinship care	9%	21%	21%	
Any unrelated foster care	1%	16%	29%	
Total number of caregiver changes				
0	97%	84%	68%	
1	2%	13%	24%	.001
≥ 2	1%	3%	8%	
In homeless shelter in first 24 mo	5%	12%	6%	.26
	<i>N</i> = 87	<i>N</i> = 68	<i>N</i> = 36	
Any child-focused intervention started				
Before 12 mo of age	7%	9%	21%	.08
From 12–24 mo of age	10%	14%	18%	
No intervention	83%	77%	61%	
In day care during first 24 mo	62%	51%	71%	.23
	<i>N</i> = 61	<i>N</i> = 49	<i>N</i> = 21	

* Mean (standard deviation).

† Averaged for each subject over first 24 months.

Unadjusted Means of BSID Scores at Each Age of Assessment by In Utero Cocaine Exposure

TABLE 6

Age at Testing	In Utero Cocaine Exposure	N	MDI	SD	N	PDI	SD
6 mo	Unexposed	85	112.9	19	85	107.5	14.8
	Lighter	62	109.6	18.4	62	104.4	14.6
	Heavier	35	113.3	18.5	35	103.3	16
12 mo	Unexposed	69	111	12.9	69	101.5	14.8
	Lighter	66	108.1	15.4	66	98.8	13.6
	Heavier	29	114.3	10.6	29	103.2	15.7
24 mo	Unexposed	76	89.8	13.9	76	102.8	15
	Lighter	57	90.7	15.8	57	101.4	14.4
	Heavier	28	93.9	16.3	28	104.1	16.7

SD indicates standard deviation.
No significant differences were found between cocaine groups within each time period.