

Cognitive and Motor Outcomes of Cocaine-Exposed Infants

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MATERNAL USE OF COCAINE during pregnancy remains a significant and enduring public health problem, particularly in urban areas of the United States and among women of low socioeconomic status.¹ An estimated 1 million children have been born after fetal cocaine exposure since the mid-1980s, when the so-called crack epidemic emerged with the availability of a cheap, potent, smokable form of cocaine.² Cocaine has effects on monoaminergic neurotransmitter systems important for the development of neuronal circuitry and human learning.³⁻⁵ A growing body of research documents relationships between prenatal cocaine exposure and prematurity,^{6,7} low birth weight,⁸ microcephaly,^{9,10} and newborn behavioral abnormalities,^{11,12} which has raised concerns regarding long-term cognitive and developmental outcomes.

There are few longitudinal studies of cocaine-exposed infants, however, and their findings are contradictory.¹³ While some studies have found generalized developmental delays in cocaine-exposed infants,¹⁴⁻¹⁶ others have not demonstrated differences.¹⁷ Still other studies, including a recent meta-analysis¹⁸,

For editorial comment see p 1990.

Context Maternal use of cocaine during pregnancy remains a significant public health problem, particularly in urban areas of the United States and among women of low socioeconomic status. Few longitudinal studies have examined cocaine-exposed infants, however, and findings are contradictory because of methodologic limitations.

Objective To assess the effects of prenatal cocaine exposure on child developmental outcomes.

Design Longitudinal, prospective, masked, comparison birth cohort study with recruitment in 1994-1996.

Setting Obstetric unit of a large US urban teaching hospital.

Participants Four hundred fifteen consecutively enrolled infants (218 cocaine-exposed and 197 unexposed) identified from a high-risk, low-socioeconomic status, primarily black (80%) population screened through clinical interview and urine and meconium samples for drug use. The retention rate was 94% at 2 years of age.

Main Outcome Measures The Bayley Mental and Motor Scales of Infant Development, assessed at 6.5, 12, and 24 months of corrected age.

Results Controlled for confounding variables, cocaine exposure had significant effects on cognitive development, accounting for a 6-point deficit in Bayley Mental and Motor Scales of Infant Development scores at 2 years, with cocaine-exposed children twice as likely to have significant delay (mental development index <80) (odds ratio, 1.98; 95% confidence interval, 1.21-3.24; $P = .006$). For motor outcomes, there were no significant cocaine effects.

Conclusions Cocaine-exposed children had significant cognitive deficits and a doubling of the rate of developmental delay during the first 2 years of life. Because 2-year outcomes are predictive of later cognitive outcomes, it is possible that these children will continue to have learning difficulties at school age.

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show only subtle cognitive effects or find deficits only when more specific areas of functioning are measured.¹⁸⁻²⁰ These studies are inconclusive for a number of reasons. Most had high rates of attrition ranging from 30% to 55%,¹⁴⁻¹⁷ often combined with small sample sizes.^{15,18,20} High attrition and small sample sizes are especially problematic in assessing teratogenic effects of fetal cocaine exposure on cognitive outcomes. Cocaine-exposed infants experience a large number of negative environmental factors known to be related to poorer child developmental outcomes that are also likely to differentially affect subject recruitment and retention.²¹ These con-

founding variables include minority race, low socioeconomic status, poor prenatal care, low maternal education and IQ, greater maternal psychological distress, a less stimulating home environment, larger family, higher risk for out-of-home placement, and maternal use of drugs in addition to cocaine, especially alcohol, marijuana, and tobacco.

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The effects of such factors must be considered before poorer child outcomes are attributed to fetal cocaine exposure²²; thus, adequate sample sizes must be used. Some studies enrolled only full-term infants or only infants who received prenatal care, perhaps restricting the samples to the least-affected infants. Moreover, in most studies, biological measures of severity of exposure, important in validating a dose-response relationship, have been lacking. Such validation is important when effects of illegal drugs such as cocaine are investigated because maternal self-report about illegal drug use can be less than candid, and such measures reflect unreliable so-called street dosages of drugs. Biological measures to establish severity of exposure more reliably^{8,23} are also important because some negative effects of cocaine have been demonstrated only with heavy exposure.^{12,15,24,25} Finally, with the exception of one study¹⁵ that found effects of heavy cocaine exposure on cognitive development at 18 months, all published studies have used the old (1969) version of the Bayley Scales of Infant Development to assess developmental outcomes.²⁶ These scales had outdated normatives that might be insensitive to drug effects.

This study followed a large cohort of cocaine-exposed infants recruited from a sample prospectively screened at birth at a large urban county hospital. They were compared with unexposed infants from the same population on standardized normative measures of cognitive and motor development until 2 years of age. Both maternal self-report measures and biological assays of cocaine and other drug metabolites in maternal urine and infant meconium were used to classify infants and measure severity of fetal exposure.

METHODS

Subjects

Mothers and infants were recruited between 1994 and 1996 at a large urban county teaching hospital and had been identified from a high-risk population screened for drug use. Urine samples were obtained immediately before or af-

ter labor and delivery from all women who received no prenatal care, appeared to be intoxicated or taking drugs, had a history of involvement with the Department of Human Services in previous pregnancies, or either admitted that they were using drugs or appeared to be at high risk for drug use after interview by hospital staff. Urine was analyzed for the presence of cocaine metabolites, cannabinoids, opiates, phencyclidine (PCP), and amphetamines by the Syva Emit method (Syva Company, Palo Alto, Calif). The specificity for benzoylecgonine was 99% at 0.3 mg/mL. Follow-up gas chromatography analyses were performed.

Infants of screened mothers also had the following meconium drug analyses for cocaine and its metabolites: benzoylecgonine, meta-hydroxybenzoylecgonine, cocaethylene, cannabinoids, opiates, PCP, amphetamines, and benzodiazepines.^{27,28} Meconium was collected in the hospital from infants' diapers and was scraped from the diaper with a wooden spatula and placed in a plastic container. Specimens from multiple diapers of the same newborn were accumulated and kept refrigerated. The entire sample was then stirred for 5 minutes to ensure homogeneity. Meconium analysis was conducted with gas chromatography-mass spectrometry. Screening assays were conducted with fluorescence polarization immunoassay (United States Drug Testing Laboratories Inc, Des Plaines, Ill). Cutoff levels for drugs of interest were as follows: cocaine and metabolites, 25 ng/g; opiates, 25 ng/g; amphetamines, 100 ng/g; PCP, 25 ng/g; and tetrahydrocannabinol, 25 ng/g. Confirmatory assays were conducted with gas chromatography-mass spectrometry operated in electron-impact selected-ion monitoring mode.

Internal validity for use of concentrations of cocaine metabolites to assess severity of prenatal exposure has been demonstrated in prior studies,²³ which found reasonable correlations between maternal self-report and meconium concentrations of benzoylecgonine (0.57), meta-hydroxybenzoylecgonine (0.51),

cocaine (0.46), and cocaethylene (0.29).²³ External validity can also be derived from these drugs' relationships to fetal and infant outcomes in this sample.^{10,12,25}

Although maternal urine and infant meconium were collected systematically, infant urine specimens were not. However, when available, they were analyzed like maternal urine specimens.

A nurse recruiter approached all screened women shortly before or after infant birth. Six hundred forty-seven mothers and their infants were identified, of whom 54 were excluded (20 cocaine positive and 34 cocaine negative). Reasons for exclusion included no meconium (15), Down syndrome (2), maternal psychiatric history (16), primary heroin use (2), being HIV positive (5), maternal low IQ (1), fetal alcohol syndrome (1), maternal age younger than 19 years (2), infant illness (3), maternal chronic illness (4), and other (3). One hundred fifty-five mothers refused to participate (49 cocaine positive and 106 cocaine negative), and 23 (9 cocaine positive and 14 cocaine negative) did not come to the enrollment visit. Mothers who refused to participate were more likely not to be cocaine users ($P < .001$) and to be younger ($P = .04$). There were no differences in race, sex, or infant birth characteristics. Therefore, 415 women and their infants enrolled in the study (218 positive and 197 negative). Cocaine-exposed infants were identified by a positive response on any of the following measures: infant meconium, urine, or maternal urine positive for cocaine; maternal report to hospital staff; or maternal self-report during clinical interview (see below). For the majority of the control subjects, all of these indicators were negative; for 11 subjects (6%), meconium was unavailable, but all other screening and follow-up indicated no evidence of infant exposure.

Procedures

Caregivers were approached as soon as possible after the infants were born, at which time the caregiver was interviewed regarding drug use. For infants

in nonmaternal care, biological mothers were interviewed separately. An adaptation of the Maternal Post-Partum Interview²⁹ quantified maternal drug use. For the month before pregnancy and during each trimester, mothers recalled frequency and amount of drug use. For tobacco, they noted the number of cigarettes smoked; for marijuana, the number of marijuana cigarettes smoked; for alcohol, the number of drinks of beer, wine, or hard liquor each day, with each drink equivalent to 0.5 mL of absolute alcohol; and for cocaine, the number of so-called rocks consumed and amount of money spent daily. For each drug, frequency of use was recorded on a Likert-type scale ranging from 0 (not at all) to 7 (daily use), which was converted to reflect the average number of days a drug was used each week. The frequency was multiplied by the amount used daily to compute a severity score for the month before pregnancy and for each trimester. This score was then averaged for a total score for the prenatal exposure for each drug.

At the neonatal visit, maternal education level and socioeconomic status were determined. Mothers were given the Peabody Picture Vocabulary Test—Revised,³⁰ the block design and picture completion subscales of the Wechsler Adult Intelligence Scales—Revised,³¹ and the Brief Symptom Inventory³² to obtain measures of maternal vocabulary, nonverbal intelligence, and psychological distress, respectively. The Brief Symptom Inventory yields a measure of overall distress, the Global Severity Index, which was used in data analyses.

Demographic and medical characteristics taken from hospital records included maternal race, age, parity, number of prenatal care visits, type of medical insurance, infant gestational age, birth weight, length, head circumference, and Apgar scores. The Hobel Neonatal Risk score³³ was computed to obtain a measure of neonatal risk condition.

At 6.5, 12, and 24 months (corrected ages), infants were tested at the research laboratory and given the Bayley Scales of Infant Development,³⁴ widely used standardized assessments

of infant development. The scales yield a Mental Development Index, a standard score reflecting memory, language, and problem-solving abilities. The Psychomotor Development Index measures gross and fine motor control and coordination. Normative data from the scales yield a mean of 100 and SD of 15. All assessors were master's level psychology assistants or the equivalent and masked to infant drug exposure. Interrater reliabilities (agreement percentage) for examiners for the scales averaged 93% (range, 77%-100%) for the Mental Development Index and 94% (range, 79%-100%) for the Psychomotor Development Index.

At each visit, the infant's placement (with biological mother or relative or foster parent) was noted, and the current caregiver data were updated to provide concurrent measures of psychological distress and tobacco, alcohol, marijuana, and cocaine use. If the infant was placed with a new caregiver, intellectual measures were also updated. At the 2-year visit, for half the sample, the Home Observation for Measurement of the Environment test (HOME)³⁵ was administered to the caregiver in an interview format as a measure of the quality of the caregiving environment. There were no significant differences on demographic, medical, or drug-use characteristics between children who were given the HOME and those who were not (all $P > .10$). By exposure group, cocaine users who received the HOME were older (30.4 vs 28.7 years; $P = .02$). For nonusers, those administered the HOME had more prenatal care visits (9.5 vs 7.6; $P = .01$), and their children had lower Apgar scores at 5 minutes (8.7 vs 8.9; $P = .02$).

This study was approved by the institutional review boards of the participating hospitals, and maternal written informed consent was obtained. All caregivers were given \$35 for participation at each visit, with transportation costs and lunch provided.

Statistical Analysis

Sample size, estimated for the outcomes of the Mental Development In-

dex and Psychomotor Index, was calculated according to our pilot data and with the 2-sample t test. To detect a 10% difference, a sample size of 98 subjects per group was needed, assuming 80% power and a significance level of .01. However, we recruited additional subjects to account for attrition.

Before analysis, drug self-report measures, the Global Severity Index, and meconium quantification variables, all positively skewed, were normalized by $\log x + 1$ transformation. Means and SDs are reported in terms of the original distribution, with transformations used in analyses.

Groups were compared on demographic variables, frequency and severity of drug use, and infant birth outcomes by using t tests for continuous data and χ^2 analyses for categorical variables. Outcomes over time were compared by using mixed model analyses (SAS PROC MIXED version 8.2; SAS Institute Inc, Cary, NC), first considering only cocaine status and then, if significant, by controlling for appropriate confounders.

Spearman rank order correlations were used to assess the relationship of severity of prenatal drug exposure measures to infant outcomes at each age. Confounding variables were entered into the MIXED model stepwise if they were significantly different between exposed and unexposed groups and related to the outcome at $P < .2$. The order of entry was designed to account for demographic, environmental, and medical factors before drug exposure factors, consistent with a teratologic model, and to reduce the number of correlated variables in the statistical model. Demographic and prenatal factors were considered first, followed by infant caregiving and environmental variables and drug exposure variables in the following order: maternal age; parity; number of prenatal care visits; maternal years of education; marital status; socioeconomic status; biological and current caregiver (time dependent) Peabody Picture Vocabulary Test—Revised, Wechsler Adult Intelligence Scale—Revised block design,

and picture completion scores; non-maternal care status; biological maternal and current caregiver (time dependent) psychological distress; and prenatal and current caregiver measures of cigarette, alcohol, and marijuana exposure. Because many of the confounding variables were expected to be correlated, they were entered stepwise into the model separately and retained only if they added significantly to the prediction of outcome. Global Severity Index was tested last because maternal psychological distress can be a precipitant and an effect of cocaine use.

Because infant birth characteristics or medical condition can be an effect of cocaine exposure, birth outcomes that differed between groups were assessed as possible mediating variables by entering them into the model after all other variables if there was a significant group effect.³⁶ Infant race and sex, which did not differ between exposure groups, were considered moderator variables, with their effects tested through interaction terms.

RESULTS

Sample Characteristics

Maternal characteristics are listed in TABLE 1. The majority of both groups were black, had a high school education or lower, had low income, and were unemployed. For all trimesters, cocaine-using women used alcohol, marijuana, and tobacco more frequently and copiously than nonusers. Cocaine users reported a mean (SD) of 23.3 (44.0) rocks of cocaine used weekly throughout pregnancy, while the median use was 7.9 units. The highest individual use throughout pregnancy in the sample was 80 cigarettes daily, 30 joints weekly, 111 drinks weekly, and 386 rocks of cocaine weekly. More detailed measures reflecting daily use by trimester have been reported.¹⁰ The means (ranges) of the concentration of cocaine metabolites in meconium were as follows: cocaine, 142 (0-3112) ng/g; cocaethylene, 18 (0-419) ng/g; benzoylecgonine, 552 (0-9998) ng/g; and methoxybenzoylecgonine, 264 (0-9998) ng/g. Cocaine-using women were

Table 1. Maternal Characteristics*

	No. (%)		P Value
	Cocaine Users (n = 218)	Nonusers (n = 197)	
Age, y			
Mean (SD)	29.6 (5.0)	25.7 (5.0)	.001
Median (range)	29 (18-41)	24 (18-41)	
Race, nonwhite	177 (81)	156 (79)	.60
Married	16 (7)	34 (17)	.002
Maternal employment	11 (5)	42 (21)	.001
Low socioeconomic status†	213 (98)	192 (98)	.63
Education <high school graduate	103 (48)	61 (31)	.001
Parity			
Mean (SD)	3.6 (2.0)	2.7 (2.0)	.001
Median (range)	3 (1-10)	2 (1-10)	
Gravida			
Mean (SD)	5.0 (2.0)	3.7 (2.0)	.001
Median (range)	5 (1-14)	3 (1-11)	
No prenatal care	44 (20)	19 (10)	.003
Prenatal visits, No.			
Mean (SD)	5.1 (5.0)	8.7 (5.0)	.001
Median (range)	4 (0-25)	9 (0-25)	
Drug use during pregnancy			
Alcohol	177 (86)	122 (65)	.001
Marijuana	102 (50)	25 (13)	.001
Tobacco	182 (88)	79 (42)	.001
Amphetamine	5 (2)	2 (1)	.31
Barbiturate	2 (1)	1 (0.5)	.62
Benzodiazepine	24 (15)	0 (0)	.001
Heroin	5 (2)	0 (0)	.03
Phencyclidine	11 (5)	0 (0)	.001
Amount of drug use during pregnancy‡			
Cigarettes/d			
Mean (SD)	11.6 (11.0)	4.4 (8.0)	.001
Median (range)	10 (0-80)	0 (0-45)	
Alcohol, drinks/wk			
Mean (SD)	9.9 (18.0)	1.3 (4.0)	.001
Median (range)	3.7 (0-111)	0 (0-33)	
Marijuana, cigarettes/wk			
Mean (SD)	1.3 (4.0)	0.6 (4.0)	.04
Median (range)	0 (0-21)	0 (0-30)	
Cocaine, rocks/wk			
Mean (SD)	23.3 (44.0)
Median (range)	7.9 (0.1-386)	...	
Cognitive tests			
PPVT-R score			
Mean (SD)	73.8 (15)	78.2 (15)	.005
Median (range)	72 (40-159)	78 (40-123)	
WAIS-R BD score			
Mean (SD)	6.8 (2.0)	7.2 (2.0)	.09
Median (range)	7 (1-14)	7 (1-13)	
WAIS-R PC score			
Mean (SD)	6.6 (2.0)	6.9 (2.0)	.09
Median (range)	6 (2-12)	6 (1-17)	
Global Severity Index			
Mean (SD)	0.81 (0.7)	0.49 (0.5)	.001
Median (range)	0.64 (0-3.76)	0.29 (0-2.9)	

(continued)

older, had more children, and were less likely to have had prenatal care. They were less likely to be married and had a less advanced vocabulary, lower block design and picture completion scores, and higher psychological distress scores.

Infant birth characteristics are listed in TABLE 2. Cocaine-exposed infants had a lower gestational age, birth

weight, head circumference, and length than unexposed infants. In the exposed group, there were more infants who were preterm, had a low birth weight, and were small for gestational age. More exposed infants were in non-maternal care just after birth (34% vs 1.5%; $P < .001$), at 1 year (46% vs 4%; $P < .001$), and at 2 years of age (50% vs 4%; $P < .001$). Exposed infants aver-

aged 0.61 nonmaternal care placements by 2 years vs 0.09 for unexposed infants ($P < .001$). There were no differences in HOME scores between the exposed and unexposed groups at 2 years.

From birth to 2 years, there were 11 deaths, 8 in cocaine-positive children and 3 in cocaine-negative children ($\chi^2 = 1.9$; $P = .17$). Causes of death for the cocaine-exposed group were sudden infant death syndrome (4), cardiopulmonary arrest (1), pneumonia (1), accidental asphyxia (1), and respiratory distress syndrome (1). Causes of death for the unexposed children were sudden infant death syndrome (2) and respiratory distress syndrome (1). Retention rates were 84% (339) at 6.5 months, 90% (364) at 12 months, and 94% (379) at 2 years, with 100% (404) of survivors having at least 1 follow-up visit.

Developmental Outcomes

To assess the effects of cocaine while controlling for confounding variables and to test for mediational effects, drug, demographic, and birth variables that related to cognitive and motor outcome within each age were examined (TABLE 3, TABLE 4, and TABLE 5). Of these, the following variables that differed by exposure group were significant predictors of longitudinal outcome (at $P = .20$) in the mixed model for Mental Development Index and thus were entered as covariates: current caregiver picture completion score ($P < .09$) and block design score ($P = .16$), birth mother picture completion score ($P < .08$) and block design score ($P = .13$), birth-mother parity ($P = .14$), and educational level ($P = .05$). In the stepwise model, current caregiver and birth mother picture completion scores and birth mother block design score were no longer significant once the current caregiver block design was controlled, and for the parsimony of the model, they were removed from the analysis. Similarly, once the HOME score was included in the model, the number of placements was no longer significant. Birth mother parity and edu-

Table 1. Maternal Characteristics* (cont)

	No. (%)		P Value
	Cocaine Users (n = 218)	Nonusers (n = 197)	
Placements, No.‡			
Mean (SD)	0.61 (0.68)	0.09 (0.45)	.001
Median (range)	1 (0-3)	0 (0-4)	
HOME score at 2 years			
Mean (SD)	29.1 (5.4)	29.7 (5.2)	.39
Median (range)	30 (13-37)	31 (7-37)	

*All *t* test comparisons are based on means. PPVT-R indicates Peabody Picture Vocabulary Test—Revised; WAIS-R, Wechsler Adult Intelligence Scale—Revised; BD, block design; PC, picture completion; and HOME, Home Observation for Measurement of the Environment. Ellipses indicate data not applicable.

†Low socioeconomic status was determined according to the Hollingshead IV and V classification.

‡For cocaine users, n = 206; for nonusers, n = 188.

§Number of infant placements at assessment age.

||For cocaine users, n = 108; for nonusers, n = 114.

Table 2. Infant Characteristics

	Maternal Cocaine Users (n = 218)	Maternal Nonusers (n = 197)	P Value
Male sex, No. (%)	102 (47)	96 (49)	.70
Gestational age, wk			
Mean (SD)	37.7 (3.0)	38.5 (3.0)	.01
Median (range)	38 (25-43)	39 (22-42)	
Pretermity (<37-wk gestational age), No. (%)	64 (29)	36 (18)	.01
Birth weight, g			
Mean (SD)	2709 (678)	3086 (703)	.001
Median (range)	2760 (755-4535)	3230 (510-4515)	
Low birth weight (<2500 g), No. (%)	79 (36)	36 (18)	.001
Very low birth weight (<1500 g), No. (%)	14 (6)	8 (4)	.28
Small for gestational age, No. (%)	26 (12)	4 (2)	.001
Birth length, cm*			
Mean (SD)	47.2 (4.0)	49.9 (4.0)	.001
Median (range)	48 (33-58)	49.5 (29-57)	
Head circumference, cm*			
Mean (SD)	32.3 (2.0)	33.4 (3.0)	.001
Median (range)	32.5 (23-37.5)	34 (19-39.5)	
Apgar score (1 min)			
Mean (SD)	8.0 (2.0)	7.9 (2.0)	.69
Median (range)	8 (1-10)	9 (1-9)	
Apgar score (5 min)			
Mean (SD)	8.8 (1.0)	8.8 (1.0)	.85
Median (range)	9 (2-10)	9 (3-10)	
Hobel Neonatal Risk score			
Mean (SD)	8.3 (19.0)	6.0 (17.0)	.19
Median (range)	0 (0-110)	0 (0-120)	

*P values adjusted for prematurity.

cational level added significantly to the model, but after these demographic factors were considered, the only drug exposure to predict outcome was cocaine. When the effects of these variables were controlled in the mixed model, cocaine exposure remained a significant predictor of cognitive outcome (TABLE 6, model 1).

Cocaine-exposed children performed more poorly on the Bayley Mental Scale than unexposed children after adjustment for significant confounding variables (TABLE 7). Although Mental Development Index scores for both groups decreased over time, children prenatally exposed to cocaine had scores that decreased faster. From 6.5 to 24 months, the average Mental Development Index score for infants exposed to cocaine declined by 14 points (SE, 1.1); for those not exposed to cocaine, by 9 points (SE, 1.1). Using a contrast of the means to test for a difference in the change from 6.5 to 24 months between the groups yielded a significant result ($|\Delta|$, 4.44; SE, 1.52; $t_{345}=2.92$; $P=.004$). At 2 years, the adjusted means difference of 6 points yielded a moderate effect size of 0.44.

These effects remained significant and had the same magnitude when race, sex, and HOME score at 2 years were controlled in the model (Table 6, model 2). Further, the effects of cocaine remained significant when all birth outcomes, Apgar scores ($P=.44$), Hobel risk ($P<.001$), and maternal Global Severity Index ($P=.91$) scores were controlled, indicating that birth outcomes were not mediators of cocaine's effects. Only the addition of birth head circumference to the model partially reduced the effect of cocaine at 2 years (from 6 points to 5.6 points), but it still did not reduce the significance of the cocaine effect ($F=9.8$; $P=.002$), indicating that some of the negative effects of cocaine exposure on cognitive outcome were mediated through smaller head circumference at birth. Interaction (effect modifiers) was also tested with significant confounding variables, as well as race, sex, and HOME score, but no interaction effects were found.

When incidence of scores in the range of mental retardation (Mental Development Index <70) at 2 years of age was compared, cocaine-exposed children were significantly more likely to be so classified, namely, 13.7% (27) of the exposed vs 7.1% (13) of the unexposed ($\chi^2_1=4.3$; $P=.04$). Mild delays (Mental Development Index <80) were present in 37.6% (74) of exposed children vs 20.9% (38) of the unexposed group ($\chi^2_1=12.6$; $P=.001$). Adjusted for the same covariates in the linear model, the odds ratio for scores in the range of mental retardation was 1.87 (95% confidence interval [CI], 0.92-3.80; $\chi^2=3.0$; $P=.08$) and for scores less than 80 was 1.98 (95% CI, 1.21-3.24; $\chi^2=7.5$; $P=.006$).

For the Psychomotor Development Index, significant effects of age, sex, and prenatal tobacco exposure, but not cocaine, were found (Table 6). Scores for both groups of children increased significantly from 6.5 months to 2 years of age (Table 7), tobacco exposure pre-

dicted lower motor scores, and boys had lower motor scores than girls.

Correlations of Meconium Metabolites With Outcomes

Spearman rank correlations of the concentration of meconium metabolites of cocaine and cognitive and motor outcomes are listed in TABLE 8. The concentration level of benzoylecgonine was negatively related to the Mental Development Index score at 6.5 months, and all cocaine metabolites except cocaine were related negatively to Mental Development Index scores at 1 and 2 years. Higher levels of benzoylecgonine and meta-hydroxybenzoylecgonine were also related to a lower Psychomotor Development Index score at 2 years.

COMMENT

Our study found significant cognitive deficits, with cocaine-exposed children twice as likely to have significant delay throughout the first 2 years of life.

Table 3. Spearman Correlations of Drug Exposure Measures With Outcomes at Each Follow-up Age*

	Mental Development Index, mo			Psychomotor Development Index, mo		
	6.5	12	24	6.5	12	24
Prenatal Maternal						
Cigarettes	-0.05	-0.10†	-0.12‡	-0.07	-0.07	-0.18§
Alcohol, drinks	0.03	-0.10†	-0.15§	0.03	-0.01	-0.12
Marijuana, cigarettes	0	-0.10†	-0.06	0.04	0.02	-0.01
Cocaine, rocks	-0.09	-0.18§	-0.20§	-0.02	-0.01	-0.11‡
Heroin use	-0.07	-0.01	-0.13§	-0.02	0	0
Benzodiazepine use	-0.09	-0.05	-0.12‡	-0.07	-0.02	-0.07
Phencyclidine	-0.09†	-0.07	-0.08	-0.06	-0.02	-0.06
Amphetamine use	-0.02	-0.03	0.03	-0.03	-0.03	0.03
Current Caregiver						
Cigarettes, birth	-0.03	-0.01	-0.11‡	-0.04	-0.02	-0.15‡
Cigarettes	0.06	-0.02	-0.09†	-0.04	-0.02	-0.14§
Alcohol, birth	0.06	-0.04	-0.11‡	0.08	-0.03	-0.10†
Alcohol	0.12‡	-0.03	0.07	0.11‡	0	-0.01
Marijuana, birth	0.03	-0.06	-0.02	0.10†	0.05	-0.01
Marijuana	0.10†	0	-0.05	0.09	0.01	0.04
Cocaine, birth	-0.12‡	-0.11‡	-0.16‡	-0.05	0.01	-0.09†
Cocaine	0.03	-0.06	-0.16§	-0.06	0.01	-0.03

*Cigarette use based on mean daily consumption; alcohol, marijuana, and cocaine use based on mean weekly consumption.

† $P<.10$.

‡ $P<.05$.

§ $P<.01$.

||Time dependent: refers to the measurement of postnatal drug use by the current caregiver as self-reported at each follow-up age.

The 13.7% rate of mental retardation is 4.89 times higher than that expected in the population at large, and the percentage of children with mild or greater delays requiring intervention was 38%, almost double the rate of the high-risk noncocaine- but polydrug-exposed comparison group. Because 2-year Mental Development Index scores are predictive of later cognitive outcomes, it is possible that these chil-

dren will continue to have learning difficulties at school age.^{37,38}

Cognitive delays could not be attributed to exposure to other drugs or to a large number of potentially confounding variables. Further, poorer cognitive outcomes were related to higher amounts of cocaine metabolites in infant meconium as well as to maternal self-reported measures of amount and frequency of cocaine use during preg-

nancy, providing further support for a teratologic model. Developing neural systems of the fetal brain may be directly affected by cocaine's adverse effects on monoaminergic system development or indirectly affected through vascular constriction with subsequent decreases in placental blood flow and generalized hypoxemia.^{4,5,39} In nonhuman primate models, fetal cocaine exposure has significant permanent effects on cortical morphology, including a reduction in the number of cortical cells, inappropriate positioning of cortical neurons, and altered glial morphology.⁴⁰⁻⁴² Cognitive impairments have been demonstrated in preclinical and human studies of cocaine exposure as well, especially in assessments of learning and memory.^{12-16,24,42,43} Selective attention in particular appears to be affected and may contribute to overall slower rates of learning in rat and human studies.^{25,43-45} In this sample, cocaine effects on cognitive outcomes were also partially mediated by lower birth head circumference, which we have demonstrated to be independently related to the level of prenatal cocaine exposure in a previous study,¹⁰ further suggesting a direct biological linkage of cocaine exposure to child behavioral outcomes.

Some limitations to this study should be considered. Although examiners were masked to infant drug status, it may have been possible to identify drug exposure through maternal or caregiver characteristics, since all children were assessed with the caregiver present. The sample was also recruited according to hospital screening measures and reflects outcomes only of more heavily exposed infants. Also, the

Table 4. Spearman Correlation of Biological Maternal Characteristics at Birth and Current Caregiver Characteristics With Outcomes at Each Follow-up*

	Mental Development Index, mo			Psychomotor Development Index, mo		
	6.5	12	24	6.5	12	24
Biological Mother at Birth						
Race	-0.02	-0.10†	-0.15‡	0.07	0.02	0.05
Infant sex	-0.11§	-0.09†	-0.20	-0.13§	-0.07	-0.19‡
Maternal age	-0.02	-0.08	-0.10†	-0.01	-0.01	-0.01§
Parity	-0.05	-0.10§	-0.14‡	-0.13§	-0.11§	-0.06
Prenatal visits	0.22	0.15‡	0.06	0.25‡	0.14‡	0.08
Maternal education	0.08	0.05	0.14‡	0.04	0.08	0.11§
Marital status	0.03	0.01	0.10†	-0.03	0	0.10§
PPVT-R score	0	0.06	0.10†	-0.02	-0.03	0
WAIS-R BD score	0.05	0.12§	0.10†	0.02	-0.02	0.03
WAIS-R PC score	0.01	0.07	0.14‡	-0.10	-0.01	0.03
Global Severity Index	-0.10†	-0.11§	-0.12§	-0.01	-0.03	-0.06
Current Caregiver						
PPVT-R score, birth	-0.02	0.03	0.07	-0.09	-0.06	-0.04
PPVT-R score¶	-0.04	-0.02	0.07	-0.09	-0.06	-0.08
WAIS-R BD score, birth	0.07	0.11§	0.11§	0	-0.03	0.06
WAIS-R BD score¶	0.03	0.09	0.10†	-0.03	-0.06	0.02
WAIS-R PC score, birth	0.02	0.03	0.14‡	-0.01	-0.02	0.02
WAIS-R PC score¶	0.02	0.02	0.14‡	0	-0.02	0.03
Global Severity Index, birth	-0.08	-0.02	-0.06	0.06	0.06	-0.01
Global Severity Index¶	0.02	-0.02	-0.08	0.07	0.01	0.01
HOME score (n = 223)	0.18§	0.18§	0.37	0	-0.03	0.12†
Placements	-0.14§	-0.08	-0.11§	-0.11†	-0.05	-0.14‡

*See Table 1 for expansions of abbreviations.

†P<.10.

‡P<.01.

§P<.05.

||P<.001.

¶Time dependent.

Table 5. Spearman Correlations of Birth Outcomes With Development Indices

Outcome	Mental Development Index						Psychomotor Development Index					
	6.5 mo	P Value	12 mo	P Value	24 mo	P Value	6.5 mo	P Value	12 mo	P Value	24 mo	P Value
Gestational age	0.11	.04	0.19	.001	0.11	.04	0.05	.27	0.23	.001	0.14	.007
Birth weight	0.10	.07	0.13	.02	0.11	.04	0.02	.68	0.19	.001	0.08	.10
Birth length	0.16	.003	0.14	.007	0.13	.01	0.10	.06	0.20	.001	0.10	.05
Head circumference	0.16	.003	0.20	.001	0.18	.001	0.07	.21	0.22	.001	0.12	.03
Apgar score, 5 min	0.10	.08	0.15	.005	0.05	.38	0.01	.80	0.18	.001	0.11	.04
Hobel Neonatal Risk score	-0.18	.001	-0.21	.001	-0.09	.07	0.01	.35	-0.24	.001	-0.13	.01

drug assessments were conducted retrospectively, making reliability of maternal report problematic. In a separate study, we found that biological measures were confirmatory of self-reports, and validity of these measures was indicated by their relationship to differences in exposure groups in prior studies of this sample and to perinatal and child developmental outcomes.^{10,12,45}

Despite these limitations, the prospective enrollment, large sample size, excellent retention rates, and careful control for confounding variables support the validity of the findings. Maternal drug status was determined through biological and clinical means, enhancing reliability of classification.²³ Moreover, tobacco, alcohol, marijuana, and other drug use was quantified, reducing the likelihood that the effects of other drugs are under-controlled. These findings indicate that prenatal cocaine exposure is associated with increased risk for cognitive impairment at 2 years of age and suggest the need for public health initiatives for substance abuse prevention and treatment of pregnant women.

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REFERENCES

1. Kandel DB, Warner LA, Kessler RC. Epidemiology of drug use and abuse among women. In: Wetherington CL, Roman AB, eds. *Drug Addiction Research*

Table 6. Adjusted Effects of Cocaine Exposure on Mental and Motor Development Indices*

	Model 1			Model 2		
	df	F	P Value	df	F	P Value
Mental Developmental Index						
Prenatal cocaine exposure	1, 371	19.5	.001	1, 210	11.6	.001
Infant age	2, 355	146.6	.001	2, 202	99.0	.001
Prenatal cocaine exposure × infant age	2, 355	4.5	.01	2, 203	2.0	.13
WAIS-R block design (current caregiver at birth)	1, 359	1.6	.21	1, 210	0.1	.79
Parity	1, 360	0.9	.35	1, 208	0	.98
Biological maternal education	1, 364	3.4	.07	1, 211	1.4	.25
Infant sex				1, 208	2.0	.16
Race				1, 220	0.9	.34
HOME score				1, 216	15.4	.001
Psychomotor Development Index						
Prenatal cocaine exposure	1, 374	0.03	.87			
Infant age	2, 353	18.5	.001			
Prenatal cocaine exposure × infant age	2, 353	2.3	.11			
Infant sex	1, 375	18.5	.001			
Prenatal tobacco exposure	1, 369	6.2	.01			

*See Table 1 for expansions of abbreviations.

Table 7. Bayley Mental and Motor Outcomes by Age

	Unadjusted			Adjusted		
	Cocaine Users, Mean (SE)	Nonusers, Mean (SE)	P Value	Cocaine Users, Mean (SE)	Nonusers, Mean (SE)	P Value
Mental Development Index*						
6.5 mo	96.5 (0.6)	98.4 (0.6)	.04	96.5 (0.6)	98.0 (0.7)	.09
1 y	95.2 (0.8)	99.4 (0.8)	.001	95.2 (0.8)	99.0 (0.8)	.001
2 y	82.6 (1.0)	89.1 (0)	.001	82.7 (1.1)	88.7 (1.0)	.001
Psychomotor Development Index†						
6.5 mo	94.9 (1.0)	96.6 (1.1)	.30	96.1 (1.1)	96.4 (1.1)	.86
1 y	98.2 (1.0)	98.6 (1.1)	.77	99.7 (1.2)	98.2 (1.1)	.35
2 y	99.3 (1.0)	102.9 (1.0)	.01	100.8 (1.1)	102.6 (1.0)	.23

*Means adjusted for Wechsler Adult Intelligence Scale—Revised block design score of the current caregiver at birth and for biological maternal parity and educational level.

†Means adjusted for infant sex and prenatal tobacco exposure.

Table 8. Spearman Rank Correlations of Outcomes With Cocaine Metabolites in Meconium

Metabolite	6.5 mo	P Value	12 mo	P Value	24 mo	P Value
Mental Development Index						
No.	281		304		311	
Cocaine	-0.09	.12	-0.14	.02	-0.12	.04
Cocaethylene	-0.07	.24	-0.07	.23	-0.07	.21
Benzoyllecgonine	-0.14	.02	-0.15	.01	-0.18	.002
Meta-hydroxybenzoyllecgonine	-0.09	.12	-0.13	.03	-0.19	.001
Psychomotor Development Index						
No.	279		304		311	
Cocaine	-0.08	.20	-0.08	.15	-0.10	.07
Cocaethylene	-0.03	.61	-0.04	.48	-0.02	.71
Benzoyllecgonine	-0.09	.14	-0.10	.07	-0.13	.02
Meta-hydroxybenzoyllecgonine	-0.03	.61	-0.07	.24	-0.12	.04

- and the Health of Women. Rockville, Md: National Institutes of Health; 1998:105-130.
2. National Institute on Drug Abuse. *National Pregnancy and Health Survey: Drug Use Among Women Delivering Live Births*. Rockville, Md: National Institutes of Health; 1992. Publication 96-3819.
 3. Cregler LL, Mark H. Medical complications of cocaine abuse. *N Engl J Med*. 1986;315:1495-1500.
 4. Mayes LC. Developing brain and in utero cocaine exposure: effects on neural ontogeny. *Dev Psychopathol*. 1999;11:685-714.
 5. Volpe J. Effects of cocaine on the fetus. *N Engl J Med*. 1992;327:399-407.
 6. Chouteau M, Namerow PB, Leppert P. The effect of cocaine abuse on birthweight and gestational age. *Obstet Gynecol*. 1988;72:351-354.
 7. Singer L, Arendt R, Song LY, Warshawsky E, Kliegman R. Direct and indirect interactions of cocaine with childbirth outcomes. *Arch Pediatr Adolesc Med*. 1994;148:959-964.
 8. Zuckerman B, Frank DA, Hingson R, et al. Effects of maternal marijuana and cocaine use on fetal growth. *N Engl J Med*. 1989;320:762-768.
 9. Little BB, Snell LM. Brain growth among fetuses exposed to cocaine in utero: asymmetrical growth retardation. *Obstet Gynecol*. 1991;77:361-364.
 10. Singer LT, Salvator A, Arendt RE, Minnes S, Farkas K, Kliegman R. Effects of cocaine/polydrug exposure and maternal psychological distress on infant birth outcomes. *Neurotoxicol Teratol*. In press.
 11. Richardson GA, Hamel SC, Goldschmidt L, Day NL. The effects of prenatal cocaine use on neonatal neurobehavioral status. *Neurotoxicol Teratol*. 1996;18:519-528.
 12. Singer LT, Arendt RE, Minnes S, Farkas K, Salvator A. Neurobehavioral outcomes of cocaine-exposed infants. *Neurotoxicol Teratol*. 2000;22:1-14.
 13. Frank DA, Augustyn M, Knight WG, Pell T, Zuckerman B. Growth, development, and behavior in early childhood following prenatal cocaine exposure: a systematic review. *JAMA*. 2001;285:1613-1625.
 14. Singer LT, Arendt R, Farkas K, et al. Relationship of prenatal cocaine exposure and maternal postpartum psychological distress to child developmental outcome. *Dev Psychopathol*. 1997;9:473-489.
 15. Alessandri SM, Bendersky M, Lewis M. Cognitive functioning in 8- to 18-month-old drug exposed infants. *Dev Psychol*. 1998;18:565-573.
 16. Arendt R, Angelopoulos J, Salvator A, Singer L. Motor development of cocaine-exposed children at age two years. *Pediatrics*. 1998;103:86-92.
 17. Hurt H, Brodsky NL, Betancourt L, et al. Cocaine-exposed children: follow-up through 30 months. *J Dev Behav Pediatr*. 1995;16:29-35.
 18. Lester BM, Lagasse LL, Seifer R. Cocaine exposure and children: the meaning of subtle effects. *Science*. 1998;282:633-634.
 19. Azuma SD, Chasnoff JJ. Outcome of children prenatally exposed to cocaine and other drugs: a path analysis of three-year data. *Pediatrics*. 1993;92:396-402.
 20. Richardson GA, Conroy ML, Day NL. Prenatal cocaine exposure: effects on the development of school-age children. *Neurotoxicol Teratol*. 1996;18:627-634.
 21. Singer LT. Advances and redirections in understanding effects of fetal drug exposure. *J Drug Issues*. 1999;29:253-262.
 22. Jacobson SW, Jacobson JL. Methodological considerations in behavioral toxicology in infants and children. *Dev Psychol*. 1991;32:390-403.
 23. Arendt RA, Singer LT, Minnes S, Salvator A. Accuracy in detecting prenatal drug exposure. *J Drug Issues*. 1999;29:203-214.
 24. Jacobson SW, Jacobson JL, Sokol RJ, Martier SS, Chiodo LM. New evidence for neurobehavioral effects of in utero cocaine exposure. *J Pediatr*. 1996;129:581-590.
 25. Singer LT, Arendt RE, Fagan JF, et al. Neonatal visual information processing in cocaine-exposed and non-exposed infants. *Infant Behav Dev*. 1999;22:1-15.
 26. Bayley N. *Manual for the Bayley Scales of Infant Development*. New York, NY: Psychological Corp; 1969.
 27. Lewis D, Moore C, Leikin J. Cocaehtylene in meconium specimens. *Clin Toxicol*. 1994;32:697-703.
 28. Ostrea EM Jr, Brady MJ, Parks PM, Asensio DC, Naluz A. Drug screening of meconium in infants of drug dependent mothers. *J Pediatr*. 1989;115:474-477.
 29. Streissguth AP. *The Behavioral Teratology of Alcohol: Performance, Behavioral, and Intellectual Deficits in Prenatally Exposed Children*. New York, NY: Oxford University Press; 1986.
 30. Dunn LM, Dunn LM, Robertsong GJ, Eisenberg JL. *Peabody Picture Vocabulary Test—Revised*. Circle Pines, Minn: American Guidance Service; 1981.
 31. Wechsler D. *Wechsler Adult Intelligence Scale—Revised*. San Antonio, Tex: Psychological Corp; 1989.
 32. Derogatis L. *The Brief Symptom Inventory: Administration, Scoring, and Procedures Manual*. 2nd ed. Baltimore, Md: Clinical Psychometric Research Inc; 1992.
 33. Hobel CJ, Hyvarinen MA, Okada DM, Oh W. Prenatal and intrapartum high risk screening. I: prediction of the high risk neonate. *Am J Obstet Gynecol*. 1973;117:1-9.
 34. Bayley N. *Bayley Scales of Infant Development*. 2nd ed. San Antonio, Tex: Psychological Corp; 1993.
 35. Caldwell B, Bradley R. *Home Observation for Measurement of the Environment*. Little Rock: University of Arkansas Press; 1984.
 36. Barron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 1986;51:1173-1182.
 37. Fagan JF, Singer LT. Infant recognition memory as a measure of intelligence. In: Lipsitt L, ed. *Advances in Infancy Research*. Vol. 2. Norwood, NJ: Ablex Publishing Corp; 1983:31-78.
 38. Molfese VJ, Acheson S. Infant and preschool mental and verbal abilities: how are infant scores related to preschool scores? *Int J Behav Dev*. 1997;20:595-607.
 39. Wood JR Jr, Plessinger MA, Clark KE. Effects of cocaine on uterine blood flow and fetal oxygenation. *JAMA*. 1987;257:957-961.
 40. Lidow MS. Prenatal cocaine exposure adversely affects development of the primate cerebral cortex. *Synapse*. 1995;21:332-341.
 41. Wilkins AS, Maroba JJ, Tabit E, Kosfsky BE. Transplacental cocaine exposure, III: mechanisms underlying altered brain development. *Neurotoxicol Teratol*. 1998;20:239-249.
 42. Kosofsky BE, Wilkins AS. A mouse model of transplacental cocaine exposure: clinical implications for exposed infants and children. *Ann N Y Acad Sci*. 1998;846:248-261.
 43. Johns JM, Means MJ, Anderson DR, Bass EW, Means LW, McMillan BA. Prenatal exposure to cocaine, II: effects on open-field activity and cognitive behavior in Sprague-Dawley rats. *Neurotoxicol Teratol*. 1992;14:343-349.
 44. Strupp BJ, Morgan RE, Garavan H, Mactutus CF, Booze RM. Prenatal cocaine exposure: an emerging cognitive profile. *Neurotoxicol Teratol*. 1998;20:355.
 45. Singer LT, Arendt RA, Minnes S, Salvator A, Siegel AC, Lewis BA. Developing language skills of cocaine exposed infants. *Pediatrics*. 2001;107:1057-1064.