Cognitive Outcomes of Preschool Children With Prenatal Cocaine Exposure

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Context Because of methodological limitations, the results of the few prospective studies assessing long-term cognitive effects of prenatal cocaine exposure are inconsistent.

Objective To assess effects of prenatal cocaine exposure and quality of caregiving environment on 4-year cognitive outcomes.

Design Longitudinal, prospective, masked comparison cohort study from birth (September 1994-June 1996) to 4 years.

Setting Research laboratory of a US urban county teaching hospital.

Participants A total of 415 consecutively enrolled infants identified from a high-risk population screened for drug use through clinical interview, urine, and meconium screens. Ninety-three percent retention for surviving participants at 4 years of age resulted in 376 children (190 cocaine-exposed and 186 nonexposed).

Main Outcome Measure The Wechsler Preschool and Primary Scales of Intelligence-Revised.

Results After control for covariates, prenatal cocaine exposure was not related to lower full-scale IQ (cocaine exposed [80.7] vs nonexposed [82.9]; $P=.09$) scores or summary verbal (cocaine exposed [79.9] vs nonexposed [81.9]; $P=.11$) or performance (cocaine exposed [85.5] vs nonexposed [87.5]; $P=.18$) IQ scores at age 4 years. However, prenatal cocaine exposure was related to small but significant deficits on several subscales (mean [SE]): visual-spatial skills (cocaine exposed [7.3 (0.22)] vs nonexposed [8.2 (0.22)]; $P=.01$), general knowledge (cocaine exposed [6.1 (0.18)] vs nonexposed [6.7 (0.17)]; $P=.04$), and arithmetic skills (cocaine exposed [6.2 (0.20)] vs nonexposed [6.8 (0.20)]; $P=.05$). Prenatal cocaine exposure was also associated with a lower likelihood of achievement of IQ above normative means (odds ratio, 0.26 [95% confidence interval, 0.10-0.65]; $P=.004$). The quality of the caregiving environment was the strongest independent predictor of outcomes. Cocaine-exposed children placed in nonrelative foster or adoptive care lived in homes with more stimulating environments and had caregivers with better vocabulary scores, and they attained full-scale and performance IQ scores (83 and 87, respectively) similar to nonexposed children in biological maternal or relative care (full-scale IQ, 82; performance IQ, 88) and higher than cocaine-exposed children in biological maternal or relative care (full-scale IQ, 79; performance IQ, 84).

Conclusions Prenatal cocaine exposure was not associated with lower full-scale, verbal, or performance IQ scores but was associated with an increased risk for specific cognitive impairments and lower likelihood of IQ above the normative mean at 4 years. A better home environment was associated with IQ scores for cocaine-exposed children that are similar to scores in nonexposed children.

JAMA. 2004;291:2448-2456 www.jama.com

COCAINE READILY CROSSES THE placental and fetal brain barriers[1-3] and has a direct effect on the developing fetal brain through alterations in the central monoamine systems and an indirect effect through maternal vascular disruptions.[4] Brain glucose metabolism is decreased in animal studies of cocaine-exposed offspring, also potentially affecting neurodevelopment[5] and raising concerns about long-term cognitive outcomes.[6]

A number of methodologically sound studies have found a relationship between fetal cocaine exposure and negative child developmental outcomes in the first years of life,[7-15] although others have not.[16,17] A few studies have documented outcomes in the later preschool or early school years.[17-20] Long-term studies are important because cocaine may have "sleeper" effects that are not detectable until complex functional abilities are measurable.[21,22] Compensatory mechanisms may ameliorate negative effects,[23] while environmental circumstances may exacerbate or minimize the sequelae of early brain insults.[18,24] Findings in studies with

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adequate control over confounding variables[18-20,25] have varied significantly, including small IQ effects,[20] no IQ effects,[19] lower IQ in males only,[18] and deficits attributable to impoverished environments.[25]

Although environmental factors are known to relate to many child outcomes,[24,26] only a few studies of cocaine-exposed children control for whether children were placed in alternative care environments. Hurt et al[25] found that fewer cocaine-exposed than nonexposed children lived with their biological parents at 3 and 5 years, but that children who lived with their biological parents performed better on cognitive tests than children in foster or kinship care. Similarly, adoptive care did not enhance cognitive functioning in one study of prenatally cocaine-exposed infants,[27] but another study found that children in relative and foster care had higher IQ scores at 3 years than those living with their biological mothers.[28]

Other confounding variables considered when evaluating cocaine effects include ethnicity, low socioeconomic status, poor prenatal care, low maternal education and IQ, maternal psychological distress, larger family size, and additional drug exposure, all risk factors that tend to cluster with maternal cocaine use.[29,30] Moreover, in most studies, biological measures of severity of exposure have been lacking,[31] which is important since some negative effects of cocaine have been demonstrated only at heavier exposure thresholds.

This study followed a large cohort of cocaine-exposed infants recruited from a sample prospectively enrolled from birth at a large urban county hospital. They were compared with nonexposed infants from the same population on standardized, normative measures of cognitive development at 4 years of age after consideration of multiple confounding variables, including quality and type of caregiving. Prior studies of this sample found significant cognitive deficits attributable to cocaine exposure at 2 years of age,[26] even though the quality of the home environment was the strongest predictor of child outcome.

METHODS

Subjects

Subjects included 4-year-old children enrolled in a longitudinal study from birth (September 1994-June 1996) who had been seen for previous assessments at 6, 12, and 24 months of age.[10,14,26,32] Mothers were paid volunteers recruited from a large urban county teaching hospital from a high-risk population screened for drug use. Maternal and infant urine samples were obtained immediately before or after labor and delivery and analyzed for the presence of cocaine metabolites, cannabinoids, opiates, phencyclidine, and amphetamines. The Syva Emit method (Syva Co, Palo Alto, Calif) was used for urine analyses. Positive analyses were followed up by gas chromatography. Women at high risk for drug use due to lack of prenatal care, behavior suggesting intoxication, a history of prior involvement with the Department of Human Services, or self-admitted use were given toxicology screenings (99% of laboring women). Also, meconium was collected from infants' diapers in the hospital and analyzed for cocaine and other drug and metabolites at birth, including benzoylecgonine, meta-hydroxybenzoylecgonine, cocaethylene, cannabinoids, opiates, phencyclidine, amphetamines, and benzodiazepines.[33,34]

Screening assays were conducted using polarization immunoassay reagents (Fluorescence Polarization Immunoassay [FPIA], 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; phencyclidine, 25 ng/g; and tetrahydrocannabinol, 25 ng/g. If screening assays were positive, confirmatory assays were conducted using gas chromatography–mass spectrometry operated in electron impact selected ion monitoring mode. In our prior studies, reasonable correlations between maternal self-report and meconium concentrations of benzoylecgonine (0.57), meta-benzoylecgonine (0.51), cocaine (0.46), and cocaethylene (0.29) were found.[31]

A nurse recruiter approached all screened women shortly before or after infant birth. A total of 647 mothers and their infants were identified, of whom 54 were excluded (20 cocaine positive, 34 cocaine negative). Reasons for exclusion included no meconium (15), infant with Down syndrome (2), maternal psychiatric history (16), primary heroin use (2), HIV positive (5), maternal low IQ (1), fetal alcohol syndrome (1), maternal age younger than 19 years (2), infant medical illness (3), maternal chronic illness (4), and other (3). One hundred fifty-five women refused to participate (49 cocaine positive and 106 cocaine negative), and 23 (9 cocaine positive, 14 cocaine negative) did not come to the enrollment visit. Four hundred fifteen women and their infants enrolled in the study (218 positive, 197 negative). Cocaine exposure status was identified by a positive result on any measure: infant meconium (n=88 [46%]), infant urine (n=5 [2%]), maternal urine (n=118 [62%]), or maternal report to hospital (n=153 [81%]) or research staff (n=180 [95%]).

From birth to 4 years, there were 11 child deaths, 8 cocaine positive and 3 cocaine negative ($\chi^2=1.9$; $P=.17$). Causes of death for the cocaine-exposed children were sudden infant death syndrome (4), cardiopulmonary arrest (1), pneumonia (1), accidental asphyxia (1), and respiratory distress syndrome (1). Causes of death for the nonexposed children were sudden infant death syndrome (2) and respiratory distress syndrome (1). From enrollment at birth, the retention rate was 93% (376) for living children at 4 years. Of the 28 children who did not have test results at 4 years of age, 20 were cocaine positive. These 20 cocaine-positive children were more likely to be white, with lower Hobel risk scores[35] at birth, and to have mothers with lower scores on the picture completion subscale of the Wechsler Adult Intelli-

gence Scales-Revised (WAIS-R) than the 190 cocaine-positive participants. The 8 cocaine-negative children who did not participate had higher alcohol exposure prenatally, higher gestational age, better Apgar scores, and lower Hobel risk scores than the 186 participants. They also had lower Bayley Psychomotor Development Indices at 6 and 12 months.

Procedures

As soon as possible after infants' birth, a research assistant saw infants and caregivers. For infants in nonmaternal care, biological mothers were seen separately. Caregivers were interviewed regarding prenatal drug use.[26] To quantify maternal drug use, mothers were asked to recall frequency and amount of drug use for the month prior to and for each trimester of pregnancy. The number of tobacco cigarettes and marijuana joints smoked, and the number of drinks of beer, wine, or hard liquor per day was computed, with each drink equivalent to 0.5 oz of absolute alcohol. For cocaine, the number of "rocks" consumed and the amount of money spent per day were noted. 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 per week a drug was used, except for cigarettes used, which was collected as the number smoked per day. Frequency was multiplied by the amount used per day to compute an average use score for the month prior to pregnancy and for each trimester. This score was then averaged to obtain a total score for the prenatal exposure for each drug. The exposure measures were updated at each follow-up, yielding assessments of postnatal caregiver use for each drug.

Maternal education level and socioeconomic status were determined at the neonatal visit. The Peabody Picture Vocabulary Scale-Revised (PPVT-R),[36] the block design and picture completion subscales of the WAIS-R,[37] and the Brief Symptom Inventory[38] were given to mothers to obtain measures of maternal vocabulary, nonverbal intelligence, and psychological distress, respectively. The Global Severity Index (GSI), a summary scale of the Brief Symptom Inventory and a measure of psychological distress, was used in data analyses. Scores on the GSI range from 0 to 4, with a clinical cutoff raw score of 1.19 or higher for women not referred for psychiatric illness.

Maternal race, age, parity, number of prenatal care visits, type of medical insurance, infant gestational age, birth weight, length, head circumference, and Apgar scores were taken from hospital records. The Hobel neonatal risk total score[35] was derived from a checklist of 35 weighted neonatal health factors. Totals were summed to obtain a measure of neonatal risk condition. Scores of 10 or higher have been used in previous research to establish high-risk groups.

At 4 years of age (between September 1998 and June 2000), children were seen at the research laboratory by examiners unaware of cocaine status and administered the Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R).[39] The WPPSI-R is an individually administered, standardized, normative measure for assessing intelligence in young children, which yields an overall IQ as well as verbal and performance IQ scores. Six subscales were administered, measuring arithmetic, vocabulary, and verbal comprehension (verbal scale), and object assembly, block design, and picture completion (performance scale). Since 6 of 10 possible subscales were administered, summary IQ scores were computed based on instructions for prorating (estimating) scores. The intraclass correlations for the current sample are 0.99 for performance IQ and 0.98 for verbal IQ; they range from 0.95 (vocabulary) to 1.00 (block design).

The Home Observation of the Environment (HOME)-Preschool version[40] was administered to the caregiver in an interview format to assess the quality of the caregiving environment. For half this sample, the infant version of the HOME scale had been administered in interview format at 2 years and was related to child cognitive development ($r=0.37$; $P<.001$).[26] The intraclass correlation between 2- and 4-year HOME scores was 0.57 for this subsample. Also at 4 years, the child's placement (with biological mother or relative/foster/adoptive caregiver) was noted, and data on the current caregiver were updated to provide concurrent measures of psychological distress and drug use, including tobacco, alcohol, marijuana, and cocaine or other drug use. For new caregivers, intellectual measures were also performed.

This study was approved by the institutional review boards of the participating hospitals, and maternal caregiver written informed consent was obtained. Subjects were protected by a writ of confidentiality, which prevented the principal investigator from being forced to release any research data in which subjects are identified, even under court order or subpoena. All caregivers were given a stipend of $50, transportation costs to the laboratory, and lunches.

Statistical Analysis

Sample size for this study was calculated using data from a previous phase of the study and pilot data. To detect a 10% difference in group means, a sample size of 98 subjects per group was needed, assuming 80% power, a significance level of .01, and a 2-sample *t* test. However, additional subjects were recruited to account for attrition.

Prior to analysis, drug self-report measures, the GSI, 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 and 4-year outcomes using *t* tests and Wilcoxon Mann Whitney tests for continuous data and Pearson χ^2 or the Fisher exact test for categorical variables. The outcome measures, subscales from the WPPSI-R, were examined for distributional characteristics.

Stem-and-leaf and quantile-quantile plots demonstrated that the subscales did not substantially deviate from normality in this large sample to warrant a transformation or use of nonparametric statistical methods.

Multivariate analysis of variance (MANOVA) was conducted on the unadjusted WPPSI-R scores to assess overall group differences, followed by linear regression analyses to assess specific drug effects. Adjusted WPPSI-R scores, controlling for confounding variables demonstrated to be significant in the regression model, were calculated to compare the cocaine-exposed and nonexposed groups.

Logistic regression analyses were conducted to assess effects of cocaine on the likelihood of IQ scores in the range of mental retardation and on those above the normative mean. Associations between cocaine exposure and other predicted factors were expressed as adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Cocaine-exposed children in foster or adoptive care and biological maternal or relative care and nonexposed children were compared on environmental, drug, and outcome characteristics. Analysis of variance (ANOVA) was used to assess these comparisons. To control the overall significance level, in the event of a significant group effect, follow-up pairwise tests were performed using the Tukey test.

Spearman rank order correlations were used to assess the relationship of severity of prenatal and concurrent drug exposure measures to child outcomes. Variables significantly correlated with the outcomes at $P<.10$ were entered into the model stepwise. If, on entry, covariates were significant at $P<.10$, they remained in the model. The order of entry was designed to account for demographic, environmental, and medical factors prior to drug exposure factors, consistent with a teratologic model[21,22] and to reduce the number of redundant variables in the statistical model. Demographic and prenatal factors were considered first, followed by infant caregiving and environmental variables and drug exposure variables as follows: HOME score; maternal age; parity; number of prenatal care visits; maternal years of education; marital status; socioeconomic status; biological and current caregiver PPVT-R, WAIS-R block design, and picture completion scores; nonmaternal care and foster care status; biological maternal and current caregiver psychological distress; and prenatal as well as current caregiver measures of cigarette, alcohol, and marijuana exposure, prior to cocaine exposure.

The GSI was included last because psychological distress can be both a precipitant of and an effect of cocaine use. Because infant birth parameters or medical condition can also be affected by cocaine exposure,[10] birth outcomes, which differed between exposure groups, were assessed as possible mediating variables by entering them into the regression equation after all other variables. Infant race and sex, which did not differ between exposure groups, were considered moderator variables with their effects tested through interaction terms. A P value of $<.05$ was used to determine significance levels for all outcome variables. All analyses were performed using SAS statistical software, version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

Sample Characteristics

Women who used cocaine were older, had more children, and were less likely to have prenatal care (TABLE 1). The majority of both groups were African American of low-income status. Women who used cocaine were less likely to be married or to have completed high school, had lower vocabulary scores, and higher psychological distress scores than women who did not use cocaine.

For all trimesters, women who used cocaine also used alcohol, marijuana, and tobacco more frequently and in higher amounts than nonusers. Cocaine users averaged 24.6 (SD=46.0) "rocks" of cocaine per week over the pregnancy, with median use approximately 8.2 units. The highest average use over pregnancy reported in the sample was 80 cigarettes per day, with median use of 10; 30 joints per week with median use of 0; 111 drinks per week with median use of 3.7; and 386 "rocks" of cocaine per week. The means and ranges of the concentration (ng/g) of cocaine metabolites in meconium were as follows: cocaine, 142 (0-3112); cocaethylene, 18 (0-419); benzoylecgonine, 552 (0-9998); and metabenzoylecgonine, 264 (0-9998).

Cocaine-exposed infants were of lower gestational age, birth weight, head circumference, and length than nonexposed infants (TABLE 2), and were more likely to be preterm, low birth weight, small for gestational age, and in nonmaternal care. The median number of placements for exposed children was 1 (range, 0-7) vs 0 (range, 0-5) for nonexposed infants ($z=-9.49$ $P<.001$). The majority of the current caregivers for nonexposed children were biological mothers (95%); the remainder (5%) were adoptive (3) or foster mothers (5) or relatives (1). For the cocaine group, 55% (95) were biological parents, 12% (23) were adoptive parents, 10% (19) were foster mothers, and 23% (44) were relatives. For the 42 cocaine-exposed children who were adopted or placed in foster care, 50% (21) were in their current homes for 48 months, 12% (5) for 36 to 47 months, 24% (10) for 24 to 35 months, 7% (3) 12 to 23 months, and 7% (3) for less than 12 months. There was no group difference in preschool participation (49% [93] of cocaine-exposed children vs 44% [81] of nonexposed children). There were no group differences in HOME scores.

Developmental Outcomes

MANOVA performed on unadjusted WPPSI-R scores indicated a significant overall effect of exposure on the summary IQ and several subscale scores, with univariate effects on full-scale and performance IQs, object assembly, and information and a nonsignificant trend on verbal IQ ($P=.08$) and arithmetic ($P=.06$) (verbal, performance, and full-scale IQ: Wilks $\lambda=0.98$

[F=3.13, *df*=3, 372, *P*=.03] and for subscale scores: Wilks λ=0.95 [F=3.39, *df*=6, 368, *P*=.003]).

Adjusted Differences

In linear regression models adjusting for potential confounding variables, there was a nonsignificant trend for cocaine-exposed children to have lower full-scale IQ scores. There were no significant effects of prenatal cocaine exposure on the prorated summary verbal or performance IQ measures. However, there were specific effects of prenatal cocaine exposure on several subscales, with cocaine-exposed children having lower information, arithmetic, and object assembly scores than nonexposed children (TABLE 3). Prenatal cocaine exposure was unrelated to block design, vocabulary, and picture completion scores after controlling for covariates.

Evaluation of moderating factors yielded a significant prenatal cocaine exposure by sex interaction for arithmetic ($t[df, 363]=-2.2$, $P<.03$), indicating that only boys were adversely affected. The adjusted means of arithmetic scores are 5.4 (0.3) for cocaine-exposed boys, 6.7 (0.3) for nonexposed boys, and 6.9 (0.3) for girls regardless of the exposure. There were no moderating effects of race.

When covariates were examined, the quality of the caregiving environment was the strongest independent predictor of all outcomes. When the prorated full-scale IQ was considered, the HOME score, maternal marital status, and parity accounted for 6 IQ points in contrast to the 2.2 IQ points accounted for by cocaine exposure. There was also a significant cocaine exposure by foster or adoptive care interaction for performance and full-scale IQ scores (*t* tests [*df*, 363] ≥2.33; *P* values <.02), indicating that cocaine-exposed children in foster or adoptive care had higher scores than cocaine-exposed children in biological maternal or relative care. This effect was mediated by the environmental characteristics associated with foster or adoptive care as shown in TABLE 4. There was no difference in outcomes between nonexposed children in foster or adoptive care and those in biological maternal or relative care, but the number of children in foster or adoptive care may have been too small to detect differences (n=8). Biological maternal vocabulary and block design scores were

Table 1. Maternal and Current Caregiver Characteristics by Cocaine Status

Characteristic	Cocaine Users (n = 190)	Nonusers (n = 186)	Statistic			*P* Value
			χ^2	*t*	*df*	
Biological Maternal Categorical Variables, No. (%)						
Black race	158 (83.2)	150 (80.7)	0.4			.53
Received prenatal care	153 (80.5)	169 (90.9)	8.2			.01
Married	16 (8.4)	32 (17.2)	6.5			.01
Low socioeconomic status	185 (97.9)	182 (97.9)	0.01			.98
<High school graduate	89 (46.8)	59 (31.7)	9.0			.01
Drug use during pregancy						
Alcohol	156 (85.7)	116 (65.2)	20.6			<.001
Marijuana	89 (48.9)	23 (12.9)	54.4			
Tobacco	159 (87.4)	72 (40.5)	86.1			
Amphetamine*	5 (2.8)	2 (1.1)	1.2			.45
Barbiturate*	1 (0.6)	1 (0.65)	0.01			.99
Heroin*	4 (2.2)	0	4.0			.12
Phencyclidine*	10 (5.5)	0	10.0			.002
Biological Maternal Continuous Variables, Mean (SD)						
Age, y	29.7 (5.0)	25.6 (4.8)		–8.2	374	<.001
Parity	3.5 (1.8)	2.7 (1.8)		–4.3	374	
Gravida	5.0 (2.3)	3.6 (2.1)		–6.0	374	
No. of prenatal obstetric visits	5.2 (4.6)	8.8 (4.8)		7.4	373	
Amount of drug use during pregnancy						
Tobacco (mean No. of cigarettes per day)	11.6 (11.2)	4.1 (7.7)		–10.4	358	
Alcohol (mean No. of drinks per day × mean No. of days per week)	9.7 (17.5)	1.4 (4.6)		–10.6	358	
Marijuana (mean No. of joints per day × mean No. of days per week)	1.4 (3.5)	0.6 (3.5)		–4.3	358	
Cocaine (mean No. of rocks per day × mean No. of days per week)	24.6 (46.0)					
Test scores						
PPVT-R	73.6 (15.3)	77.9 (14.9)		2.7	360	.01
WAIS-R BD	6.9 (2.1)	7.2 (2.1)		1.4	362	.17
WAIS-R PC	6.7 (2.1)	7.1 (2.4)		1.4	362	.15
Global Severity Index	0.53 (0.73)	0.35 (0.53)		–5.2	347	<.001
Current Caregiver at 4 y Continuous Variables, Mean (SD)†						
Test scores						
PPVT-R	78.8 (17.4)	78.2 (15.5)		–0.34	350	.74
WAIS-R BD	6.8 (2.3)	7.2 (2.1)		1.6	354	.11
WAIS-R PC	6.9 (2.3)	7.0 (2.4)		0.45	354	.65
Global Severity Index	0.32 (0.38)	0.38 (0.43)		1.25	344	.21
Amount of drug use past 30 d						
Tobacco (mean No. of cigarettes per day)	7.2 (8.4)	4.4 (7.5)		–4.1	342	<.001
Alcohol (mean No. of drinks per day × mean No. of days per week)	2.4 (6.7)	2.1 (7.3)		–0.8	344	.45
Marijuana (mean No. of joints per day × mean No. of days per week)	0.2 (0.8)	0.4 (3.2)		0.9	344	.38
HOME score	42.0 (6.4)	41.7 (6.7)		–0.5	374	.64

Abbreviations: HOME, Home Observation for Measurement of the Environment; PPVT-R, Peabody Picture Vocabulary Test-Revised; WAIS-R BD, Wechsler Adult Intelligence Scale-Revised Block Design; WAIS-R PC, Wechsler Adult Intelligence Scale-Revised Picture Completion.
*Based on Fisher exact test.
†Primary female caregiver to child at 4 years of age.

also related to 4-year child IQ scores and to specific subscale abilities (Table 3). Higher caregiver psychological distress was significantly related to a child's lower fund of knowledge. There were additional covariates (Table 3) that bore first-order relationships to outcomes, but these relationships were not significant once other factors were controlled.

Mediating Variables

All birth parameters were positively related to all WPPSI-R outcomes. The Hobel neonatal risk score was negatively related to all outcomes. When birth outcomes were evaluated as potential mediators of cocaine effects, head circumference and length at birth had a partially mediating effect on the WPPSI-R arithmetic subscale score.

Environmental Effects

Because a significant percentage of cocaine-exposed children were removed from maternal care, comparisons were made of the environmental, drug, and outcome characteristics of children placed in biological relative care vs children who were in adoptive or nonrelative foster care and those who remained in biological maternal care (Table 4). Since there were no differences between those in biological maternal or relative care within the cocaine-exposed group, the 2 groups were combined. Comparisons indicated that cocaine-exposed children in foster or adoptive care lived in more stimulating home environments and their caregivers had better vocabulary scores than those of cocaine-exposed children in biological maternal or relative care and nonexposed children. In addition, cocaine-exposed children in foster or adoptive care had verbal, performance, and full-scale IQs equivalent to nonexposed children, while cocaine-exposed children in biological maternal or relative care had lower full-scale and performance IQ scores than nonexposed children, despite the fact that children in foster or adoptive care had twice the severity of cocaine exposure as measured by maternal report of the average number of "rocks" of cocaine used weekly over the pregnancy. Moreover, the duration of placement in foster or adoptive care was positively related to full-scale IQ (Spearman $r=0.30$; $P=.05$).

The percentages of children who scored in the range of mental retardation (IQ <70) and those who scored above the normative mean (IQ >100) were also examined. Cocaine-exposed children in nonrelative adoptive or foster care had the lowest occurrence of IQ scores in the range of mental retardation (10%) and were similar to nonexposed children (16%). Cocaine-exposed children in biological maternal or relative care had the highest rate of mental retardation (25%) and differed

Table 2. Infant Birth Characteristics

	Cocaine Users (n = 190)	Nonusers (n = 186)	Statistic			P Value
			χ^2	F	*t*	
Categorical variables, No. (%)						
Male sex	85 (44.7)	90 (48.4)	0.2			.48
Prematurity (<37 wk gestational age)	55 (30.0)	35 (18.8)	5.3			.02
Low birth weight (<2500 g)	70 (36.8)	34 (18.3)	16.2			<.001
Very low birth weight (<1500 g)*	12 (6.3)	7 (3.8)	1.3			.26
Small for gestational age	24 (12.8)	4 (2.2)	15.2			<.001
Continuous variables, mean (SD)						
Birth weight, g†	2700 (645.3)	3103 (696.1)		38.6		<.001
Birth length, cm†	47.3 (3.9)	49.1 (3.7)		18.7		
Head circumference, cm†	32.2 (2.1)	33.5 (2.4)		26.0		
Gestational age, wk	37.8 (2.8)	38.5 (2.8)			2.4	.02
Apgar score						
1 min	8.0 (1.4)	7.9 (1.7)			–0.5	.62
5 min	8.8 (0.6)	8.8 (0.7)			–0.1	.93
Hobel Neonatal Risk score, mean (SD)‡	7.5 (16.6)	5.8 (15.7)			–1.1	.29

*Groups were matched for very low birth weight.
†Comparison was adjusted for gestational age using analysis of covariance.
‡Hobel Neonatal Risk score derived from checklist of 35 weighted neonatal health factors. Scores of 10 or higher have been used to establish high-risk groups.

Table 3. Adjusted Wechsler Preschool and Primary Scales of Intelligence-Revised Scores at 4 Years*

	Cocaine Users (n = 190)	Nonusers (n = 186)	F	*df*	P Value
Chronologic age, y	4.1 (0.18)	4.1 (0.19)	0.06	1, 374	.81
Verbal IQ†	79.9 (0.87)	81.9 (0.88)	2.6	3, 372	.11
Information‡	6.1 (0.18)	6.7 (0.17)	4.2	4, 341	.04
Arithmetic§	6.2 (0.20)	6.8 (0.20)	3.9	3, 360	.05
Vocabulary†	7.6 (0.18)	7.6 (0.18)	0.0	3, 372	.99
Performance IQ‖	85.5 (1.03)	87.5 (1.03)	1.8	5, 356	.18
Object assembly¶	7.3 (0.22)	8.2 (0.22)	8.4	5, 356	.01
Block design#	7.3 (0.16)	7.7 (0.17)	2.3	2, 373	.13
Picture completion**	8.4 (0.24)	8.6 (0.25)	0.13	4, 370	.72
Full-scale IQ**	80.7 (0.92)	82.9 (0.93)	2.9	4, 371	.09

*Data are presented as mean (SE). The following additional variables that did not remain in the model because they were not significant at $P<.10$ were evaluated: presence of foster/adoptive care; years of biological maternal education; number of prenatal care visits; average tobacco, alcohol, and marijuana use during pregnancy; and current caregiver average tobacco use.
†Adjusted for Home Observation for Measurement of the Environment (HOME) test and parity.
‡Adjusted for HOME, parity, and current caregiver psychological distress.
§Adjusted for HOME and biological maternal Wechsler Adult Intelligence Scale-Revised Block Design.
‖Adjusted for HOME, parity, biological maternal marital status, and Peabody Picture Vocabulary Test-Revised (PPVT-R) at birth.
¶Adjusted for HOME, parity, biological maternal marital status, and PPVT-R at birth.
#Adjusted for HOME.
**Adjusted for HOME, parity, and biological maternal marital status at birth.

Table 4. Comparisons of Key Environmental Characteristics That Mediate Child Outcomes, by Caregiver Group*

Characteristic	Cocaine Exposed			Statistic			*P* Value
	Model 1: Biological Maternal/Relative (n = 148)	Model 2: Foster/Adoptive (n = 42)	Model 3: Nonexposed (n = 186)	F	*df*	χ^2	
Prenatal cocaine exposure†	20 (36)	39 (70)		4.8	1, 188		.02
Environmental characteristics							
HOME score	41 (6)	45 (5)	42 (7)	7.9	2, 373		.001‡
Current caregiver PPVT-R score	76 (16)	89 (18)	78 (15)	8.4	2, 349		.001‡
Current caregiver Global Severity Index	0.35 (0.4)	0.22 (0.2)	0.38 (0.4)	2.2	2, 343		.12
Child unadjusted outcomes							
Verbal IQ	79 (12)	83 (9)	82 (13)	3.1	2, 373		.05§
Performance IQ	84 (15)	87 (13)	88 (15)	3.0	2, 373		.05‖
Full-scale IQ	79 (13)	83 (10)	83 (14)	3.8	2, 373		.02‖
Full-scale IQ >100, No. (%)	7 (5)	1 (2)	23 (12)			8.5	.01¶
Full-scale IQ <70, No. (%)	37 (25)	4 (10)	30 (16)			6.9	.03#

Abbreviation: PPVT-R, Peabody Picture Vocabulary Test-Revised.
*Data are presented as mean (SD) unless otherwise indicated.
†Mean number of "rocks" per day × mean number of days per week.
‡Model 2 differs from models 1 and 3.
§No difference by group.
‖ Model 1 differs from model 3.
¶Model 1 differs from model 3; combined models 1 and 2 differ from model 3.
#Model 1 differs from models 2 and 3; model 2 does not differ from model 3.

from both exposed children in foster or adoptive care and from nonexposed children. When the 3 groups were compared on the percentage of children with IQ higher than 100, a lower percentage (5%) of cocaine-exposed children in biological or relative care or foster or adoptive care (2%) scored higher than 100 than the nonexposed group (12%). When logistic regression was used to assess risk factors predicting IQ scores higher than 100, after control for confounding factors of the HOME environment and biological maternal vocabulary, cocaine-exposed children were 74% less likely to achieve an IQ score above the normative mean than the control group (adjusted OR=0.26 [95% CI, 0.10-0.65]; *P* = .004).

Relationships of Meconium Metabolites With Outcomes

Relationships between the concentration of meconium metabolites of cocaine and test outcomes were also computed, with control for confounding variables. Full-scale IQ higher than 100 was inversely related to the concentration of benzoylecgonine (OR=0.71 [95% CI, 0.51-1.00]; *P*=.05). Metahydroxybenzoylecgonine was also negatively related to verbal IQ (β=–0.55, SE=0.31, *P* = .08) and arithmetic score (β=–0.16, SE=0.7, *P* = .03).

COMMENT

After controlling for confounding variables, prenatal cocaine exposure was not associated with lower full-scale, verbal, or performance IQ scores at age 4 years, but did predict significant deficits in specific cognitive skills underlying intellectual functioning and attenuated the incidence of IQ scores above the normative mean, even for children in better home environments. Further, higher concentrations of cocaine metabolites in infant meconium were significantly related to lower verbal IQ and arithmetic scores. Importantly, however, the quality of the caregiving environment appeared to have substantial compensatory effects on cocaine-exposed children placed in adoptive or foster care. Cocaine-exposed children placed in adoptive care achieved performance similar to nonexposed children living in less stimulating, lower socioeconomic status home environments. Indeed, environmental intervention through foster or adoptive care was associated with a lower likelihood of mental retardation among cocaine-exposed children, despite heavier drug exposure.

In the same cohort at 2 years of age, cocaine exposure per se had a larger effect size on cognitive outcome, raising the possibility that drug effects may diminish over time, especially in the context of environmental interventions. Alternatively, the prorated WPPSI-R assessment at 4 years of age may be less sensitive than the 2-year evaluation.

Our findings are consistent with and expand on other studies of preschool cocaine-exposed children in which specific but not global IQ deficits were found. Bennett et al,[18] using a different IQ measure, found lower IQs for 4-year-old boys who were exposed prenatally to cocaine and specific deficits in working memory and quantitative reasoning for both boys and girls. In the current study, quantitative skills were also affected, albeit only in boys, and the largest effects for both sexes were found on object assembly, a task requiring visual-spatial skills related to mathematical competence. The latter finding is consistent with studies in which rats treated with cocaine during the period corresponding to the third trimester in humans had impaired spatial learning.[5,41,42]

The acquisition of general knowledge was also negatively affected in cocaine-exposed children. Cocaine may affect later learning by negatively regulating neuronal path finding and ultimately synaptic activity through disruption of dopaminergic and nor-

adrenergic systems prenatally.[43] Dopaminergic and noradrenergic innervation within the ventral hippocampus can disrupt spatial working memory and attentional processes necessary for learning and test performance.[44] Our prior studies found that prenatal cocaine exposure predicted poorer visual and auditory attention and recognition memory in the first year of life[10,14,45] and decrements in general cognitive functioning at 2 years.[26]

Of significant interest is the influence of the more stimulating caregiving environments of children adopted or placed in nonrelative care on the performance of cocaine-exposed children. These children had measurably better home environments and better educated, more intelligent caregivers than both nonexposed children and exposed children in biological family care, and these environmental attributes were associated with better child performance. Foster or adoptive care was also associated with a lower occurrence of mental retardation despite heavier prenatal exposure, suggesting that early environmental intervention can prevent mental retardation for some cocaine-exposed infants.

Moderating effects of sex were apparent as arithmetic skills were negatively affected in boys only. Similarly, only boys showed IQ deficits in the study by Bennett et al[18] of cocaine-exposed children at 4 years of age, consistent with research indicating that boys may be differentially vulnerable to prenatal insults.

While substances other than cocaine had first-order relationships with WPPSI-R outcomes, they disappeared once confounders were controlled. The absence of a relationship of tobacco and alcohol to outcomes is specific to the WPSSI-R at 4 years on this sample. However, we have detected alcohol, tobacco, and marijuana effects on other outcomes at different ages.[10,14,26]

The psychological distress of the caregiver was negatively related to children's acquired fund of knowledge, extending previous findings of a relationship of maternal mental health to children's development.[45,46] Maternal psychological distress was also related to poorer fetal growth[10] and attentional abnormalities in the neonatal period[14] in this sample. These findings underscore the importance of considering the effects of additional risk factors, particularly maternal mental health, on the development of cocaine-exposed infants. Substance-abusing women have high rates of comorbid psychological disorders,[10,47] and their combined risk jeopardizes the cognitive development of their children.

The current study has several advantages that may have increased the likelihood of detecting significant drug effects. Maternal drug status was determined through both biological and clinical means, enhancing the reliability of classification.[31] Moreover, other drug use was quantified, reducing the likelihood that the effects of other drugs were undercontrolled. Infants were prospectively recruited at birth, and characteristics of caregivers were carefully documented at each follow-up visit.

This study has several limitations. Since drug assessments were conducted retrospectively, the reliability of maternal report may have been affected. In a separate study, however, we found that measures of meconium concentration confirmed maternal self-report.[31] Another limitation was that only the prorated form of the WPPSI-R was administered, restricting the range of cognitive functions assessed. The partial assessment of cognitive ability may have been less sensitive than the full version. Also, the placement of a substantial number of cocaine-exposed children into more environmentally stimulating homes was unanticipated. Because the nonexposed comparison group was initially selected to control for the negative environmental effects associated with cocaine exposure in prior studies, the control group may not have had an adequate representation of more advantaged environments, and some drug effects may have been masked. We do not have information on quality of day care or preschool or other interventions. Finally, since the sample was drawn from a high-risk population in one city, the results cannot be generalized without confirmation.

Despite the above limitations, the prospective enrollment, large sample size, excellent retention, masked evaluations, and careful control for confounding variables in this study support the validity of the findings. These findings indicate that prenatal cocaine exposure is associated with an increased risk for specific cognitive impairments and a lower likelihood of above average IQ at 4 years of age. In addition, our findings underscore the beneficial effects of environmental intervention in the prevention of mental retardation for cocaine-exposed children. Drug treatment and education for this population of pregnant women, along with intensive intervention for their offspring, are essential to help maximize the future well-being of these families.

Author Contributions: As principal investigator, Dr Singer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Singer, Short, Arendt, Farkas, Klein, Russ.
Acquisition of data: Singer, Minnes.
Analysis and interpretation of data: Singer, Minnes, Short, Arendt, Farkas, Lewis, Min, Kirchner.
Drafting of the manuscript: Singer, Minnes, Lewis, Klein, Min.
Critical revision of the manuscript for important intellectual content: Singer, Minnes, Short, Arendt, Farkas, Lewis, Russ, Kirchner.
Statistical expertise: Singer, Min, Kirchner.
Obtained funding: Singer.
Administrative, technical, or material support: Singer, Minnes, Short, Arendt, Klein.
Supervision: Singer.
Funding/Support: This study was supported by grants RO1-07259 and 07957 from the National Institute on Drug Abuse and General Clinical Research Center Grant RR00080.
Role of the Sponsor: The National Institute on Drug Abuse had no role in the design and/or the conduct of the study, in the collection, analysis, or interpretation of the data, or in the preparation of the manuscript. The research design was submitted for review through the National Institutes of Health peer review process and has been conducted in accordance with National Institutes of Health guidelines.
Acknowledgment: Thanks are extended to the participating families, Phil Fragassi, MD, Laurel Schauer, PhD, and The Center for the Advancement of Mothers and Children at MetroHealth Medical Center, especially Sally Reeves, PhD, and Nancy Diffenbacher, RN, and the Cuyahoga County Department of Children's Services; Terri Lotz-Ganley for manuscript preparation; and Kristen Weigand, MA, Laurie Ellison, MSW, Selena Cook, LISW, Julia Noland, PhD, Paul Weishampel, BA, Martin Manuel, MA, Astrida Seja Kaugars, PhD, and Teresa Linares, BA, for research and data analytic assistance.

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