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Gender and alcohol moderate prenatal cocaine effects on teacher-report of child behavior☆

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Abstract

Prenatal cocaine exposure has been associated with behavior problems at school age. However, the correspondence between use of cocaine and alcohol during pregnancy is often high, making appropriate allocation of variance and control for other exposures and their interactions difficult. Additionally, gender-specific effects are not typically reported. The purpose of the current study was to determine the degree to which gender-specific effects of prenatal cocaine exposure on teacher-reported child externalizing behavior problems were evident when evaluated in relation to prenatal alcohol exposure. Subjects were singleton infants of mothers who were prospectively evaluated during pregnancy. At age seven, 499 children (214 exposed prenatally to cocaine) were evaluated in our laboratory and teacher reports were solicited. Analyses stratified by gender and prenatal alcohol exposure status, and controlled for significant pre- and postnatal confounders, revealed that among boys with prenatal alcohol exposure, those with persistent cocaine exposure throughout pregnancy had significantly higher levels of Delinquent Behavior compared to boys with no cocaine exposure. Boys with any prenatal cocaine exposure were twice as likely as unexposed boys to have clinically significant Externalizing Behavior scores. However, no association was found between prenatal cocaine exposure and scores on Externalizing Behavior and specific syndromes for boys with no prenatal alcohol exposure. Among girls with no prenatal alcohol exposure, those with persistent cocaine exposure had significantly higher levels of Externalizing Behaviors and Aggressive Behaviors compared to girls with no prenatal cocaine exposure after control for confounding, and were almost five times as likely to have clinically significant Externalizing Behavior scores. However, for girls with prenatal alcohol exposure, no association between prenatal cocaine exposure and scores on Externalizing Behavior and specific syndromes was found after control for confounding. The current findings support gender- and alcohol-moderated effects of prenatal cocaine exposure on school-age teacher-reported child behavior problems. These findings are similar to what we have reported for independent parent-reported behavioral evaluation.

Keywords: Prenatal cocaine; Prenatal alcohol; Child behavior; Gender differences

1. Introduction

Despite the success of public health campaigns, children are still being born exposed to cocaine [30]. In our urban University obstetrical center, the incidence of prenatal cocaine exposure in the mid-1980s exceeded 30% [26]. While predicted dire effects on a whole generation have not

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been realized nationally [15], lack of widespread catastrophe does not mean exposed children are spared long-term negative outcomes. Moderate to large exposure level-dependent prenatal cocaine associations with early childhood outcomes have been found [16], and we have reported significant relations between prenatal cocaine exposure and age 6–7 under-controlled behavior [8], speech and language problems [9], and growth restriction [5]. We have also found an association between persistent exposure and specific behavior problems for boys [10], while girls with any prenatal cocaine exposure were more argumentative and had achievement deficits [6].

One of the critical tasks in studying the outcomes of prenatal cocaine exposure is dealing with prenatal exposure to other substances including alcohol, cigarettes, and other illicit drugs. When other prenatal exposures are controlled, especially alcohol, the high correspondence between cocaine and alcohol use may result in a nonsignificant unique effect of cocaine on outcomes. For example, we found that while significant correlations exist between prenatal cocaine exposure and child behavioral outcomes, many of these relations are no longer significant after control for prenatal alcohol exposure [8]. In our sample, 90% of women who used cocaine also admitted to alcohol use during pregnancy. Hence, because of this high concordance between cocaine and alcohol use, it may be difficult to find unique effects, even when they exist, with typical analyses controlling for confounders.

An alternate method of data analysis, used by Fried and Watkinson [17,18] and discussed by Mattson et al. [23], involves including potentially confounding variables in an ANCOVA, followed by a factorial analysis examining the main and interaction effects of variables previously treated as confounders. This type of analysis addresses the additional possibility of a nonadditive effect, or interaction, between two exposures such as cocaine and alcohol. However, the degree of correspondence between the two exposures may still reduce the power to identify a significant interaction. In addition, the nature of the nonadditive effect, and which exposure is more salient in predicting an outcome, cannot be easily determined with this approach. For these reasons, we present stratified analyses that examine the effects of cocaine exposure separately for children exposed or not exposed to alcohol. This allows us to further examine the relations between cocaine exposure and child behavior problems independent of prenatal alcohol exposure. As we reported elsewhere for parent report of child behavior, analyses stratified by prenatal alcohol exposure reveal gender- and alcohol-specific behavioral outcomes related to prenatal cocaine exposure [32].

The aim of the current study was to investigate additional teacher-reported behavioral outcomes predicted from prenatal cocaine exposure and not evident in our prior data analyses without stratification. Briefly, we had found associations between prenatal cocaine exposure and child behavior, but many relations were no longer significant after control for prenatal alcohol exposure potentially due to high levels of confounding. In addition, we had found associations to be different for boys and girls [6,10]. In the current report, we explored an alternate method of data analysis that would allow us to determine the degree to which teacher-reported gender-specific externalizing behaviors are associated with cocaine in our sample, findings not clearly evident before because of the substantial colinearity between prenatal cocaine and alcohol exposure.

2. Methods

2.1. Subjects

All mothers in this study received prenatal care in the antenatal clinics at Wayne State University and participated in a prospective pregnancy study approved by the IRB. The pregnancy study screened over 2400 women annually and enrolled more than 600 each year based on a rectangular sampling distribution to over-sample exposed pregnancies. Those enrolled were interviewed throughout pregnancy at each prenatal visit about drug and alcohol use. Urine was collected at visits and at delivery as clinically indicated (see below). Since mothers with no prenatal care could not be evaluated prospectively in the clinic, they were necessarily excluded from our potential sample. The need for this exclusion was unfortunate, because cocaine-abusing mothers are more likely to avoid prenatal care. However, this design decision was made to balance the risks of misclassification of cocaine exposure status and inadequate assessment of other prenatal exposures (including alcohol, tobacco and other drugs) among women who delivered with no prenatal care.

Children in this study were the singleton infants delivered between September 1, 1989 and August 31, 1991 to the women extensively screened for in-pregnancy drug and alcohol use. Because over 90% of antenatal clients were African American, the study sample was limited to this racial group because of the inadequate representation of other groups. At follow-up 6–7 years later, families were intensively sought by telephone, mail or home visit to the last known address. Client files of all Detroit-based University-affiliated hospitals and the pediatric, internal medicine ambulatory services were searched for updated contact information. Telephone numbers were also searched. Exclusions included births to women known to be HIV positive, non-African American, multiple births, repeat deliveries to enrolled women, children with major congenital malformations, or children who had died. A final requirement for enrollment was that the family had to be in the Detroit Metropolitan area at age 6–7. The potential study sample consisted of 665 families. These 665 families did not differ significantly on any birth or demographic characteristics from the remaining women and children in the parent study.

2.2. Procedures

Children and parents (or primary caretaker when biologic mother was unavailable) were evaluated following the date of the child's expected entry into first grade. After informed consent, the child and caregiver were tested in our research facility. Trained research assistants, blinded to exposure status, interviewed each child and mother independently. Permission to obtain assessments from teachers was requested. Child behavior was evaluated with the Achenbach Teacher Report Form (TRF) [2]. Another assistant, also blind to prenatal exposure status, collected teacher data. Mailings were sent to each teacher and, when forms were not returned by mail, an appointment was made to collect teacher reports.

2.3. Measures

2.3.1. Prenatal cocaine (and other substance) exposure

Women were interviewed at their first prenatal visit (timing varied by subject) to ascertain an initial dichotomous self-report of cocaine exposure. Maternal urine was also tested, as clinically indicated. A trained research assistant administered a standardized, structured research interview based on Khavari and Douglass [21] to elicit estimates of level of cocaine use (times/day, days/month, and cost/month). Similar data were collected for other drugs including heroin, marijuana, and opiates. The assistants also interviewed women at each subsequent prenatal visit regarding alcohol use and drug use. Recall of alcohol use was linked to specific drinking habits (including time of day and day of week) and included information on binge drinking, as well as consumption for the two preceding weeks. Retrospective alcohol intake data was collected for the periconceptional period at the first prenatal visit. Intake was converted to ounces (oz) of absolute alcohol per day based upon the type of alcoholic beverage(s) consumed. A variable was calculated to estimate daily alcohol consumption across pregnancy. Summary variables were created to estimate frequency of drug use across pregnancy as well as the proportion of visits at which use of a specific drug was reported. Tobacco exposure was estimated from maternal report of number of cigarettes smoked in the periconceptional period, as well as across pregnancy. At delivery, urine samples from mothers and infants were screened for drug exposure when evidence (history or biologic) of past or current drug or alcohol use existed.

Three levels of prenatal cocaine exposure were defined based upon history and laboratory tests: None, Some, and Persistent. Women were considered to have cocaine exposure if they had any of the following: maternal pregnancy history of use of cocaine from the prospective structured research interviews conducted throughout pregnancy; information from the prenatal or neonatal record (maternal admission of use); positive maternal urine at any time during pregnancy; positive neonatal urine or meconium sent from the nursery. Meconium analyses were not performed until near the end of the subject recruitment period, and were available for <20% of the sample. At the 6-year follow-up, women were also queried regarding prior cocaine use. At that follow-up, an additional 13 mothers retrospectively admitted, for the first time, to using cocaine during the study pregnancy. These children were also considered to be cocaine-exposed.

From all cocaine-exposed subjects (n=214), a subset of 29 children with "persistent prenatal exposure" was identified by continued cocaine use up until delivery as evidenced by positive maternal and/or infant urine testing at delivery. Hospital policy from 1989–91 mandated maternal pregnancy and delivery urine drug screens and infant urine drug screens at delivery if there was a past history of maternal drug or alcohol use, known or suspected drug or alcohol exposure during the index pregnancy, or no prenatal care. Urine testing was performed with the Syva Emit method (Syva, Palo Alto, CA). Sensitivity for cocaine and its metabolites (ecgonine, benzoylecgonine) was <35 ng/ml (given a 95% confidence interval, 35 ng/ml is the lowest concentration that can be detected as reliably different from 0). Urine samples were collected by nursing staff and sent directly to the hospital toxicology laboratory for analysis. The cutoff level for a positive screen was 300 ng/ml. All positive screens were verified with a second Emit procedure. This hospital standard of maternal/infant urine testing at delivery resulted in screening >90% of our exposed sample.

We elected to identify women with biological evidence of late pregnancy cocaine use as a high risk group with likely across-pregnancy exposure of the fetus (cf. Ref. [10]). While it is certainly possible that a woman could use cocaine for the first time just days before delivery, given the nature of cocaine addiction and the contemporary social and legal climate, it is more likely that only those who used cocaine regularly and were unable to abstain from use would have had a positive biological measure of cocaine exposure at delivery. To support this contention, we analyzed the urine and self-report cocaine exposure data for the 29 mothers in our cohort identified as having persistent use (20 of these with complete teacher and other data are included in the current report). Among the 29 mothers whose infants had a positive urine screen at birth, only 2 women denied cocaine use around the time of conception and data were missing for 3 others, all of whom initiated care in the third trimester. One of the women who denied use admitted to daily exposure to individuals using crack cocaine and had a positive test at her only prenatal visit as well as at delivery. The other woman who denied use had a positive test for cocaine only at the end of pregnancy. Among the women for whom conception data were missing, all three admitted to significant use ("daily", "two to three times per week", or "heavy") at their first prenatal visit at 28 to 34 weeks gestation. In addition, all three of these women were no longer the primary caregiver at follow-up. The remaining 24 women also admitted to second and/or third

trimester use during pregnancy in addition to the positive delivery test. Of the 29, only 3 women initiated care in the first trimester with the majority (N=16) beginning care in the third trimester. Although we identified both early and late pregnancy use for the majority of these women, due to the known limitations of methods used to identify cocaine exposure, it is not certain that every woman used cocaine in all three trimesters. It is also possible that late pregnancy exposure per se, not "Persistent" exposure is a specific risk factor for poor outcome.

2.3.2. Achenbach Teacher Report Form (TRF)

This widely used teacher-report instrument consists of a total problem score and 8 syndrome scales [2]. Teacher completion takes less than 15 min. The syndrome scores are further grouped into Externalizing Behaviors (Delinquent and Aggressive) and Internalizing Behaviors (Withdrawn, Somatic Complaints, Anxious-Depressed). Three syndromes (Social, Thought, and Attention Problems) fit neither group. Clinically significant (grouped) syndrome scores can also be derived based on recommended cutoffs [2]. For this report, only externalizing behaviors were examined, as teachers are typically a poor source of information about child internalizing problems [4]. Raw scores were used for most analyses reported below, with the exception of those addressing clinical significance that relied on T-scores (i.e., scores standardized according to TRF manual criteria).

2.3.3. Control variables

Pregnancy and neonatal data were available, including information on other prenatal exposures (alcohol, cigarettes, other illicit drugs) using previously detailed methods [8, 20] and briefly described above. At age 6–7, the trained research assistants used a structured interview to assess prenatal and postnatal family drug, alcohol and cigarette use. Lab testing included demographic information, caregiver self-reported psychopathology [11], caregiver reported social support [25], family socioeconomic status [19], child IQ [34], maternal IQ [14], child whole blood lead level, and child report of violence exposure [29].

2.4. Statistical analyses

All variables (Tables 1 and 2) were checked for possible normality violations, and bivariate relations were assessed with ANOVAs and chi-square analysis. All analyses below used an ordinal variable, incorporating self-report and lab data, to represent prenatal cocaine exposure: no exposure, some exposure, and Persistent exposure as described above. Power analysis revealed adequate power ($1-\beta>0.80$) to identify moderate effect sizes in the outcomes with subjects divided into 6 categories (2 alcohol, 3 cocaine) for each gender. Final multiple and logistic regression analyses controlled for potential confounding variables. The three-group cocaine variable was re-coded to two dummy variables for regression analyses: no cocaine vs. any cocaine, and no/some cocaine vs. persistent cocaine). Follow-up factorial analysis of variance to test the significance of identified interactions also controlled for confounding. Selected control/confounder variables were those that correlated ($p<0.10$) with either exposure or any outcome(s), and are listed in the footnote of Table 2. Control variables were entered stepwise into regression equations, followed by the forced entry of prenatal cocaine exposure variables on the final step. Prenatal marijuana

Table 1
Comparison of cocaine exposed children with nonexposed children

Background characteristics	Nonexposed N=212	Some exposure N=130	Persistent exposure N=20	p
Infant Characteristics				
Birth weight (g)	3130±570	2832±699	2579±750	<0.001[a,b,c]
Gestational age (weeks)	39.0±2.3	38.1±3.1	37.8±4.2	0.001[b]
Apgar at 1 min	7.6±1.5	7.3±2.0	7.1±1.9	NS
Apgar at 5 min	8.7±.83	8.6±1.7	7.1±1.9	NS
Maternal characteristics				
Cigarettes during pregnancy (#/day)	5.2 ±8.0	12.5 ±9.3	10.1±9.8	<0.001[a,b]
Alcohol during pregnancy (oz abs alcohol/day)	.08±.11	.24±.21	.32±.43	<0.001[a,b]
Age at child's birth (years)	23.6±6.2	28.2±5.0	29.6±3.6	<0.001[a,b]
Family characteristics at 6-year follow-up				
Biological mother is primary caretaker (%)	91	73	72	<0.001[a,b]
Marital status of caretaker (% married)	27	24	28	NS
Family SES (Hollingshead)	29.5±9.3	28.0±8.6	30.4±8.5	NS
Years of caregiver education	11.8±1.7	11.6±2.3	11.8±1.5	NS
Family income (median)	$15,000–$19,999	$15,000–$19,000	$15,000–$19,000	NS

Values represent means±standard deviations, or percentages where indicated. Significance levels correspond to ANOVAs, or to chi-squares in the case of categorical variables. Post hoc analyses to examine specific group differences for continuous variables were Tukey's HSD at $p<0.05$, and pairwise chi-square analyses at $p<0.05$ for categorical variables.

[a] Nonexposed significantly different from some exposure group.

[b] Nonexposed significantly different from persistent exposure group.

[c] Some exposure group significantly different from persistent exposure group.

exposure was not entered as a potential confounder due to a high correspondence with cocaine exposure (almost 70% of those who reported marijuana use during pregnancy also used cocaine), and because of a lack of significant relations with outcomes.

3. Results

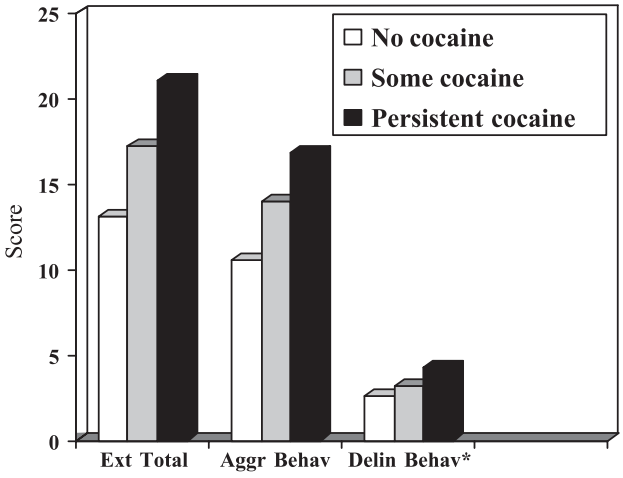
3.1. Sample

Of the 665 child–parent dyads eligible for study, 94% (626) agreed to participate. However, 40 subjects (6%) missed multiple testing appointments, and these subjects, as well as those with limited child testing (n=30; 4%) were eliminated from further analysis. The remaining study sample consisted of 556 subjects. The mothers of participants (N=556) were significantly older and had had more children than those (N=109) who did not participate. However, the two groups of children did not differ significantly on any newborn characteristics, and the mothers did not differ on use of cigarettes, alcohol, or cocaine use during pregnancy. Although teacher compliance was 90%, no reports were available for 57 subjects. The remaining 499 subjects (age range 5.9 to 7.9 years, mean=6.9), 285 controls and 214 children exposed to cocaine prenatally, constitute the basis for this report.

As we have described in previous reports [8] and as presented in Table 1, women in our sample who used cocaine during pregnancy had multiple risk factors. Cocaine users were older and used more alcohol and cigarettes during pregnancy than did control mothers. Additionally, although the cocaine-exposed children were smaller at birth and had shorter gestational duration, exposed infants did not differ from controls on 1- or 5-min Apgar scores. At the 6-year follow-up, prenatal cocaine-exposed children were less likely to be in the care of their biological mother. The marital status of the primary caretaker did not differ between groups, with only a quarter of caregivers in either group married. There was no difference between cocaine-using and control caregivers on education status or income, with both groups having a mean education of less than a high school diploma and a median yearly income of <$20,000.

3.2. Bivariate and multivariate analyses

For the full sample of 499 subjects, no significant differences were found among the three cocaine exposure groups on TRF Externalizing Behaviors, or the Aggressive Behavior and Delinquent Behavior syndromes. Analyses stratified by both gender and alcohol exposure status revealed a different picture, however. As can be seen in Fig. 1, among boys with prenatal alcohol exposure (N=191), boys with persistent cocaine exposure had significantly higher levels of Delinquent Behavior than boys with no cocaine exposure, after control for confounders. As shown in Table 2, prenatal cocaine exposure accounted for >2% of the unique variance in Delinquent Behavior, after control for confounding. However, among boys with no prenatal alcohol exposure (N=57), no significant cocaine group differences on the TRF scales of interest were evident. It should be noted, however, that conclusions about amount of



* Persistent cocaine exposure group significantly different from no cocaine exposure group after control for confounding (p<.05).
N=191
Potential control variables entered stepwise: prenatal cigarette exposure, paternal drug and alcohol use at conception, birth weight, maternal age, custody status and changes by age 6-7, drug and alcohol use in the home at age 6-7, and violence exposure.

Fig. 1. Raw TRF scores by cocaine exposure status for boys with prenatal alcohol exposure.

Table 2
Stepwise regression results for TRF externalizing behaviors

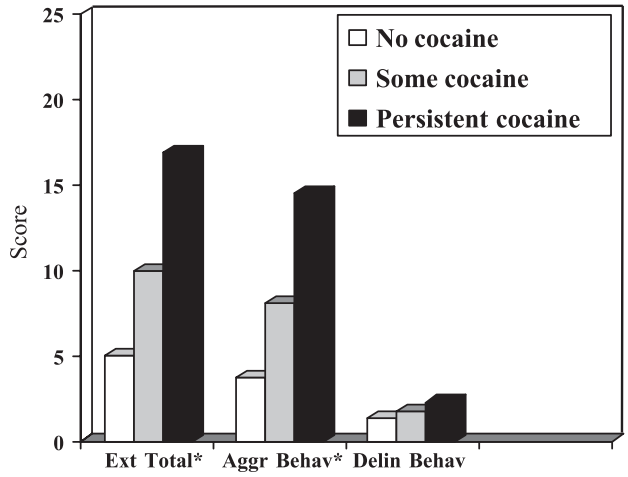
Outcome predictor	R	R^2 change	t	p
Boys with prenatal alcohol exposure				
Externalizing total				
Community violence exposure	.194	.038	2.55	0.012
Current drug exposure	.257	.028	1.96	0.051
Ordinal cocaine exposure	.284	.015	1.70	0.091
Delinquent Behavior				
Community violence exposure	.182	.033	2.43	0.016
Ordinal cocaine exposure	.234	.021	2.03	**0.043**
Boys without prenatal alcohol exposure				
Externalizing total				
Prenatal cigarette exposure	.372	.138	−2.44	0.020
Ordinal cocaine exposure	.394	.017	.85	0.403
Girls with prenatal alcohol exposure				
Externalizing total				
No significant control variables				
Ordinal cocaine exposure	.064	.004	−.74	0.464
Girls without prenatal alcohol exposure				
Externalizing total				
No significant control variables				
Ordinal cocaine exposure	.303	.092	2.46	**0.017**
Aggressive behavior				
No significant control variables				
Ordinal cocaine exposure	.328	.107	2.69	**0.009**

Potential control variables for stepwise entry: prenatal cigarette exposure, paternal drug and alcohol use at conception, birth weight, maternal age, custody status and changes by age 6–7, drug and alcohol use in the home at age 6–7, and violence exposure.

prenatal cocaine exposure cannot be made for the group of boys with no prenatal alcohol exposure since none of these boys were in the Persistent exposure group. However, those non-alcohol-exposed boys with Some cocaine exposure did not differ from those with No exposure on any of the behavioral outcomes. Despite the apparent differential cocaine effect on behavior as a function of alcohol exposure status, follow-up factorial analysis of variance resulted only in a non-significant alcohol by cocaine interaction effect for boys (p>0.05 for both Externalizing Behaviors and Delinquent Behavior).

As also presented in Table 2, significant cocaine group differences were evident after control for confounding for girls. Among those girls with no prenatal alcohol exposure (N=62), girls with Persistent cocaine exposure had significantly higher levels of Externalizing Behaviors and Aggressive Behaviors compared to girls with no cocaine exposure (see Fig. 2). Prenatal cocaine exposure accounted for over 9% of Externalizing Behavior variance, and for almost 11% of the variance in Aggressive Behavior, after control for confounding (see Table 2). However, among girls with prenatal alcohol exposure (N=189), no significant cocaine group differences on the TRF scales of interest were evident. This alcohol by cocaine exposure interaction was significant in factorial ANOVAs for both Aggressive Behavior (F(2,245)=4.53, p=0.012) and Total Externalizing Behaviors (F(2,245)=3.70, p=0.026). However, despite the apparent differential patterns of effects for boys and girls, factorial ANOVAs including all subjects and controlling for significant confounders, produced nonsignificant three-way interactions for gender by cocaine exposure by alcohol exposure (p>0.05).

To address the clinical significance of the findings for alcohol exposed boys and non-alcohol exposed girls, Externalizing Behavior scores were collapsed into two



* Persistent cocaine exposure group significantly different from no cocaine group after control for confounding (p<.05).
N=62
Potential control variables entered stepwise: prenatal cigarette exposure, paternal drug and alcohol use at conception, birth weight, maternal age, custody status and changes by age 6-7, drug and alcohol use in the home at age 6-7, and violence exposure.

Fig. 2. Raw TRF scores by cocaine exposure status for girls with prenatal alcohol exposure.

groups: those at or above the clinically significant cut-point of a *T*-score of 60, and those below 60 [2]; it should be noted that scores in the 60–63 range are considered "borderline," and for purposes of these analyses have been included as clinically significant. Among boys with prenatal alcohol exposure, after control for confounding, those with any prenatal cocaine exposure (Some or Persistent groups) were almost twice as likely as those with no prenatal cocaine exposure to have Externalizing Behavior scores above this cut-point level (48% vs. 28%, $p<0.005$). Among girls with no prenatal alcohol exposure, those with any prenatal cocaine exposure were almost five times as likely as those with no prenatal cocaine exposure to have Externalizing Behavior *T*-scores at or above 60 (53% vs. 11%, $p<0.001$), after control for confounding.

4. Discussion

Gender- and alcohol-exposure specific teacher reported behavioral effects of prenatal cocaine exposure were evident in this sample of inner-city African American children. Among boys with prenatal alcohol exposure, prenatal cocaine exposure was associated with increased levels of teacher reported externalizing problems. Exposure level-dependent effects were noted specifically for Delinquent Behaviors. Among girls without prenatal alcohol exposure, persistent prenatal cocaine exposure was associated with increased levels of teacher-reported total Externalizing Behaviors and Aggressive Behavior. While we have previously reported similar, but weaker, teacher-reported behavioral effects for boys when including prenatal alcohol exposure as a control variable [8], this report and our stratified analysis of parent-reported behavior in the same sample is the first time we have noted substantial behavioral effects related to prenatal cocaine exposure for girls. Only by stratifying by prenatal alcohol exposure were the effects on externalizing behaviors associated with prenatal cocaine exposure evident for girls.

As we have detailed elsewhere [8], there are several limitations of our study. Exclusion of children whose mothers did not receive prenatal care, and the inclusion of only African American families both limit the generalizability of our current findings. Additionally, possible misclassification of cocaine exposure status, underreporting of prenatal alcohol exposure, and the varied timing of the first pregnancy interview resulting in a varied-length recall period for drug use, may all affect the validity of our results. However, the availability of ordinal cocaine data, the use of both self-report and biological assessment of prenatal exposure, a large sample size, the inclusion of many potentially confounding factors, and stratification of analyses by both gender and alcohol exposure status are clearly strengths of this study.

The conclusions drawn from the current analyses are supported by our findings related to caregiver report of child behavior. We recently reported [32] that for girls without prenatal alcohol exposure, ordinally measured prenatal cocaine exposure was significantly related to caregiver-reported externalizing behaviors, after control for confounding. We found no evidence of a caregiver-reported externalizing behavioral effect for girls with prenatal alcohol exposure, or for boys either with or without prenatal alcohol exposure, after control for confounding. While a trend for an effect in boys with alcohol exposure was noted in the current report, the similarity in findings for girls across our two reports is striking, with the important caveat, of course, that due to small cell sizes and significant confounding, the cocaine by alcohol interaction effect was not significant. Whether behavior was rated by teachers or caregivers, increased prenatal cocaine exposure was associated with increases in externalizing behaviors among girls without prenatal alcohol exposure, but not among girls with prenatal alcohol exposure. The consistency in the effect across different behavioral raters and situations (home vs. school), coupled with the significant cocaine by alcohol interaction effect for girls, strengthens our confidence in our conclusion that prenatal alcohol exposure moderates the effects of prenatal cocaine exposure on child externalizing behavior.

A few aspects of the current findings unrelated to prenatal cocaine exposure warrants mention. First, there were several preexisting differences among the prenatal cocaine exposure groups. As has been reported in numerous studies [1,3,24,31], children exposed prenatally to cocaine weighed less at birth and had shorter gestational duration. Additionally, they were more likely to be exposed postnatally to cigarettes and cocaine, and less likely to be living with their biological mother. These findings reiterate that when examining the potential effects of prenatal cocaine exposure, it is imperative that other exposures, birth outcomes, and family variables be considered. Second, it is interesting that compared with boys, for girls there were no other variables that correlated with externalizing behavior. For boys, several control variables entered the regression equations, including community violence exposure, current drug exposure, and prenatal cigarette exposure. These findings are consistent with other reports that have suggested that the behavior of boys is more likely to be negatively impacted by prenatal and postnatal environmental influences than the behavior of girls.

The current findings support the exposure level-dependent effects of prenatal cocaine exposure on child behavior. Most of the significant relations reported here revealed significant effects of Persistent prenatal cocaine exposure. Had cocaine exposure been treated as a dichotomous variable, significant relations would have been missed. Indeed, studies such as those conducted by Richardson et al. [28] have not demonstrated a link between dichotomously evaluated prenatal cocaine exposure and externalizing behaviors at age 6. Yet, other studies, including our own, have demonstrated a negative "dose–response" relation between prenatal cocaine exposure and infant and early

childhood behavior [7,22,24,33]. Given the results of these studies, as well as the current findings, it is critical to consider the level and/or pattern of cocaine exposure when examining the association between prenatal cocaine exposure and behavior problems into childhood and beyond.

The present results also support the gender-specific effects of prenatal cocaine exposure on child behavior. Many previous researchers, examining the effects on boys and girls together, have failed to find a link between prenatal cocaine exposure and externalizing behavior problems into childhood [1,3,27]. However, we recently found gender-specific effects of prenatal cocaine exposure on multiple outcomes at early school age. We noted significant effects on externalizing behavior related to prenatal cocaine exposure for boys [8], and achievement deficits associated with exposure only for girls [6]. While the differential patterns of effects described in the current report were not supported by a significant gender by alcohol by cocaine interaction (likely due to the small cell sizes for boys and the limited power to test a three-way interaction), the stratified analysis findings suggest that the combined effect of alcohol and cocaine on behavior may be different for boys and girls. It is possible that were other researchers to examine boys and girls separately, behavior problems related to prenatal cocaine exposure would become evident. The animal literature provides additional evidence of differential effects of prenatal exposures on males and females [12,13].

The current findings raise some interesting questions. Why, for example, would the relation between prenatal cocaine exposure and behavioral outcomes vary at different levels of alcohol exposure? Is it that one effect of prenatal alcohol exposure is to alter the response to prenatal cocaine exposure? And more puzzling, why would relations be evident only among boys with prenatal alcohol exposure, and only among girls without such exposure? Alcohol and cocaine, when introduced prenatally, have been hypothesized to produce synergistic effects on dopamine transport sites [31]. For boys, our findings are most consistent with a synergistic explanation, with the most deleterious effects evident among those exposed to both alcohol and cocaine. However, the lack of a significant cocaine by alcohol interaction for boys encourages a cautious interpretation. For girls, however, it appears that exposure to either substance has a negative effect, and that exposure to an additional substance does not substantially alter the effect. Why this gender difference occurs is unclear and is not discernible from the design of the current study. However, animal studies have revealed gender differences in glucose metabolic activity in highly dopaminergic innervated brain regions in response to prenatal cocaine exposure [12]. This is one possible mechanism, although there are likely other possibilities as well. Clearly, additional work is necessary to validate the current results as well as to explore possible mechanisms for the differential combination effect of prenatal cocaine and alcohol exposure on boys and girls. Additionally, the current report suggests several ways to reduce the risk of Type II error, including the partialing of variance among exposures through stratification, the use of ordinal rather than dichotomous exposure variables, and by performing analyses separately for boys and girls.

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References

[1] V.H. Accornero, C.E. Morrow, E.S. Bandstra, A.L. Johnson, J.C. Anthony, Behavioral outcome of preschoolers exposed prenatally to cocaine: role of maternal behavioral health, J. Pediatr. Psychol. 27 (3) (2002) 259–569.

[2] T.M. Achenbach, Manual for the Teacher Report Form/4-18 and 1991 Profile, Burlington, VT, University of Vermont, 1991.

[3] S.D. Azuma, I.J. Chasnoff, Outcome of children prenatally exposed to cocaine and other drugs: a path analysis of three-year data, Pediatrics 92 (3) (1993) 396–402.

[4] M.J. Briggs-Gowan, A.S. Carter, M. Schwab-Stone, Discrepancies among mother, child, and teacher reports: examining the contributions of maternal depression and anxiety, J. Abnorm. Child Psychol. 24 (6) (1996) 749–765.

[5] C.Y. Covington, B. Nordstrom-Klee, J. Ager, R.J. Sokol, V. Delaney-Black, Birth to age 7 growth of children prenatally exposed to drugs. A prospective cohort study, Neurotoxicol. Teratol. 24 (4) (2002) 489–496.

[6] C.Y. Covington, B. Nordstrom, J. Ager, J. Janisse, R.J. Sokol, V. Delaney-Black. Academic achievement of first graders prenatally exposed to cocaine. Nursing Research, in press.

[7] V. Delaney-Black, C. Covington, E. Ostrea, A. Romero, D. Baker, M.T. Tagle, B. Nordstrom-Klee, M.A. Silvestre, M.L. Angelilli, C. Hack, Prenatal cocaine and neonatal outcome: evaluation of dose-response relationship, Pediatrics 98 (4) (1996) 735–740.

[8] V. Delaney-Black, C. Covington, T. Templin, J. Ager, B. Nordstrom-Klee, S. Martier, L. Leddick, R.H. Czerwinski, R.J. Sokol, Teacher-assessed behavior of children prenatally exposed to cocaine, Pediatrics 106 (4) (2000) 782–791.

[9] V. Delaney-Black, C. Covington, T. Templin, T. Kershaw, B. Nordstrom-Klee, J. Ager, N. Clark, A. Surendran, S. Martier, R.J. Sokol, Expressive language development of children exposed to cocaine prenatally: literature review and report of a prospective cohort study, J. Commun. Disord. 33 (6) (2000) 463–481.

[10] V. Delaney-Black, C.Y. Covington, B. Nordstrom, J. Ager, J. Janisse, J.H. Hannigan, L. Chiodo, R.J. Sokol, Prenatal cocaine: quantity of exposure and gender moderation, J. Dev. Behav. Pediatr. 25 (4) (2004) 254–263.

[11] L.R. Derogatos, R.S. Lipman, L. Covi, SCL-90: an outpatient psychiatric rating scale: preliminary report, Psychopharmacol. Bull. 9 (1973) 13–28.

[12] D.L. Dow-Edwards, L.A. Freed, T.H. Milhorat, Stimulation of brain metabolism by perinatal cocaine exposure, Brain Res. 470 (1) (1988) 137–141.

[13] D.L. Dow-Edwards, L.A. Freed-Malen, H.E. Hughes, Long-term alterations in brain function following cocaine administration during

the preweanling period, Brain Res. Dev. Brain Res. 72 (2) (1993) 309–313.
[14] L.M. Dunn, L.M. Dunn, Peabody Picture Vocabulary Test-Revised, American Guidance Service, Circle Pines, MN, 1981.
[15] K. Elliot, D. Coker, Crack babies: here they come, ready or not, J. Instr. Psychol. 18 (1991) 60–64.
[16] D.A. Frank, M. Augustyn, W.G. Knight, T. Pell, B. Zuckerman, Growth, development, and behavior in early childhood following prenatal cocaine exposure: a systematic review, JAMA 285 (12) (2001) 1613–1625.
[17] P.A. Fried, B. Watkinson, 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol, J. Dev. Behav. Pediatr. 11 (2) (1990) 49–58.
[18] P.A. Fried, B. Watkinson, Visuoperceptual functioning differs in 9- to 12-year olds prenatally exposed to cigarettes and marihuana, Neurotoxicol. Teratol. 22 (1) (2000) 11–20.
[19] A.B. Hollingshead, Four factor index of social status. New Haven, CT:Yale University, Department of Social Work, 1975 (unpublished paper).
[20] M. Kaplan-Estrin, S.W. Jacobson, J.L. Jacobson, Neurobehavioral effects of prenatal alcohol exposure at 26 months, Neurotoxicol. Teratol. 21 (5) (1999) 503–511.
[21] K.A. Khavari, F.M. Douglass, The drug use profile (DUP): an instrument for clinical and research evaluations for drug use patterns, Drug Alcohol Depend. 8 (2) (1981) 119–130.
[22] J.C. Martin, H.M. Barr, D.C. Martin, A.P. Streissguth, Neonatal neurobehavioral outcome following prenatal exposure to cocaine, Neurotoxicol. Teratol. 18 (6) (1996) 617–625.
[23] S.N. Mattson, K.E. Calarco, C.D. Chambers, K.L. Jones, Interaction of maternal smoking and other in-pregnancy exposures. Analytic considerations, Neurotoxicol. Teratol. 24 (3) (1999) 359–367.
[24] C.E. Morrow, E.S. Bandstra, J.C. Anthony, A.Y. Ofir, L. Xue, M.L. Reyes, Influence of prenatal cocaine exposure on full-term infant neurobehavioral functioning, Neurotoxicol. Teratol. 23 (6) (2001) 533–544.
[25] J.S. Norbeck, A.M. Lindsay, V.L. Carrieri, The development of an instrument to measure social support, Nurs. Res. 30 (1981) 264–269.
[26] E.M. Ostrea, M. Brady, S. Gause, A.L. Raymundo, M. Stevens, Drug screening of newborns by meconium analysis: a large-scale, prospective, epidemiologic study, Pediatrics 89 (1) (1992) 107–113.
[27] L. Phelps, N.V. Wallace, A. Bontrager, Risk factors in early child development: is prenatal cocaine/polydrug exposure a key variable? Psychol. Sch. 34 (3) (1997) 245–252.
[28] G.A. Richardson, M.L. Conroy, N.L. Day, Prenatal cocaine exposure: effects on the development of school-age children, Neurotoxicol. Teratol. 18 (6) (1996) 627–634.
[29] J.E. Richters, P. Martinez, The NIMH community violence project: I. Children as victims of and witnesses to violence, Psychiatry 56 (1993) 7–20.
[30] D.A. Savitz, L. Henderson, N. Dole, A. Herring, D.G. Wilkins, D. Rollins, J.M. Thorp Jr., Indicators of cocaine exposure and preterm birth, Obstet. Gynecol. 99 (3) (2002) 458–465.
[31] L.T. Singer, R. Arendt, S. Minnes, K. Farkas, A. Salvator, Neurobehavioral outcomes of cocaine-exposed infants, Neurotoxicol. Teratol. 22 (5) (2000) 653–666.
[32] B.G. Sood, B. Nordstrom Bailey, C. Covington, R.J. Sokol, J. Ager, J. Janisse, J.H. Hannigan, V. Delaney-Black, Gender and alcohol moderate caregiver reported child behavior after prenatal cocaine, Neurotoxicol. Teratol. 27 (2005) 191–201 (this issue).
[33] E.Z. Tronick, D.A. Frank, H. Cabral, M. Mirochnick, B. Zuckerman, Late dose–response effects of prenatal cocaine exposure on newborn neurobehavioral performance, Pediatrics 98 (1) (1996) 76–83.
[34] D. Wechsler, Wechsler Preschool and Primary Scales of Infant Intelligence—Revised Manual, The Psychological Corp, San Antonio, TX, 1989.