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## Association of Environmental Toxicants and Conduct Disorder in U.S. Children: NHANES 2001-2004

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**Title: Association of Environmental Toxicants and Conduct Disorder in U.S. Children:  
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**Running Head:** Environmental Toxicants and Conduct Disorder

**Key Words:** Conduct disorder, cotinine, epidemiology, lead poisoning, NHANES, tobacco smoke

**Abbreviations:**

CBCL: Child Behavior Checklist  
CD: Conduct Disorder  
CDC: Centers for Disease Control and Prevention  
CI: Confidence Interval  
DISC: Diagnostic Interview Schedule for Children  
DSM-IV: Diagnostic and Statistical Manual, Fourth Edition  
ETS: Environmental Tobacco Smoke  
LOD: Limit of Detection  
MEC: Mobile Examination Center  
 $\mu\text{g}/\text{dL}$ : micrograms per deciliter  
NHANES: National Health and Nutrition Examination Survey  
 $\text{ng}/\text{mL}$ : nanograms per milliliter  
NIMH: National Institute for Mental Health  
ODD: Oppositional Defiance Disorder  
OR: Odds Ratio  
PIR: Poverty to Income Ratio  
US: United States of America

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## **Section Outline**

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## **Abstract**

*Objective:* The purpose of this study was to examine the association of tobacco smoke and environmental lead exposure with conduct disorder (CD).

*Methods:* The National Health and Nutrition Examination Survey 2001-2004 (NHANES) is a nationally representative cross-sectional sample of the non-institutionalized US population. We examined the association of prenatal tobacco, postnatal tobacco, and environmental lead exposure with CD in 8-15 year old children (n=3081). Prenatal tobacco exposure was measured by parent report of cigarette use during pregnancy while postnatal tobacco was measured using serum cotinine levels. Lead exposure was assessed using current blood lead concentration. Parents completed the Diagnostic Interview Schedule for Children (DISC) to determine whether their children met DSM-IV CD criteria.

*Results:* Overall, 2.06% of children met DSM-IV criteria for CD in the past year, equivalent to 560,000 US children age 8 to 15 years old. After adjustment, prenatal tobacco exposure was associated with increased odds for CD (OR: 3.00; 95% CI: 1.36, 6.63). Increased blood lead levels (4<sup>th</sup> vs. 1<sup>st</sup> quartile) and serum cotinine levels (5<sup>th</sup> vs. 1<sup>st</sup> quintile) were associated with an 8.64-fold (95% CI: 1.87, 40.04) and 9.15-fold (95% CI: 1.47, 56.90) increased odds of meeting DSM-IV CD criteria. Increasing serum cotinine levels and blood lead levels were also associated with increased prevalence of CD symptoms (symptom count ratio lead: 1.73; 95% CI: 1.23, 2.43; symptom count ratio cotinine: 1.97; 95% CI: 1.15, 3.40).

*Conclusions:* These results suggest that prenatal tobacco exposure and environmental lead exposure contribute substantially to CD in US children.

## **Introduction**

Conduct disorder (CD) is characterized by persistent behavioral patterns that violate social rules and the rights of individuals (APA 2000). Children with CD display aggression towards people and animals, intentionally destroy other's property, and chronically steal or deceive. Children with CD are at increased risk for drug and alcohol abuse, antisocial personality disorder, and anxiety-related disorders (Goldstein et al. 2006; Gunter et al. 2006). Public expenditures related to general and mental health care, school services, and juvenile justice for children with CD exceed \$10,000 per child per year (Foster and Jones 2005).

The national prevalence of CD is unknown. It is estimated from community based regional samples that 0.4 to 3.3% of children and adolescents have CD, with males 2 to 3 times more likely than females to receive a CD diagnosis (Lahey et al. 2000; Loeber et al. 2000; Maughan et al. 2004). Prior variation in CD prevalence estimates may be related to the informant, diagnostic instrument, DSM version used (III, III-R, or IV), participants' age, socioeconomic status, and degree of urbanicity (Loeber et al. 2000). To date, no studies have provided an estimate of the national prevalence of CD in US children using DSM-IV criteria.

Questions also persist about the underlying risk factors for the development of CD (Burke et al. 2002). Prenatal tobacco smoke exposure has been consistently associated with disruptive behavior disorders, such as oppositional defiant disorder (ODD) and CD, even after controlling for potential confounders, including sociodemographic factors, prenatal insults, and parental psychopathology (Fergusson et al. 1993; Fergusson et al. 1998; Wakschlag et al. 1997; Wakschlag et al. 2002; Weissman et al. 1999). Results from a prospective cohort in New Zealand indicate that children exposed to tobacco smoke *in utero* had CD symptom rates approximately 2 times higher than unexposed children (Fergusson et al. 1998). Another

prospective study of approximately 6,000 Finnish males found that prenatal tobacco smoke exposure was associated with a 1.74-fold increased odds of committing a delinquent act in late childhood or early adulthood (Rantakallio et al. 1992).

While prior studies have documented associations between prenatal tobacco smoke exposure and CD, the relationship between postnatal environmental tobacco smoke (ETS) exposure and CD is less clear (Fergusson et al. 1998; Weitzman et al. 1992). Weitzman et al. (1992) reported significant increases in the number of behavior problems among children whose mothers smoked only after pregnancy. Compared to children of non-smoking women, children exposed to postnatal ETS had a 2-fold increased odds of having extreme behavior problems on the Behavior Problem Index of the Child Behavior Checklist (CBCL) (Weitzman et al. 1992). Similarly, in a New Zealand cohort, Fergusson reported an increased number of CD symptoms among children exposed to postnatal ETS (Fergusson et al. 1998). To date, none of these studies have used a biomarker of tobacco smoke exposure to measure the association between ETS and behavior problems. This limitation can result in exposure misclassification, since a substantial proportion of women who report no ETS exposure have measurable cotinine levels (DeLorenze et al. 2002).

The relationship between environmental lead exposure and violent, aggressive, and oppositional behavior was first reported by Elizabeth Lord and Randolph Byers (Byers and Lord 1943). They observed that among 20 lead poisoned children, 19 who had “recovered” from lead poisoning failed high school or had behavioral problems. Since then, elevated bone and blood lead levels have been associated with an increased risk of juvenile delinquency in late childhood and early adulthood in case-control and prospective cohort studies (Dietrich et al. 2001; Needleman et al. 2002; Needleman et al. 1996). Earlier studies observed children with higher

blood lead levels than the levels currently seen; thus, inferences may not be directly relevant to contemporary children with lower blood lead levels (Dietrich et al. 2001; Needleman et al. 2002; Needleman et al. 1996). Additionally, recent studies have observed associations between blood lead levels below the current Centers for Disease Control and Prevention (CDC) recommended action level of 10  $\mu\text{g}/\text{dL}$  and cognitive and behavioral deficits (Braun et al. 2006; Lanphear et al. 2005). It is unclear whether lower blood lead levels are associated with more severe behavioral problems such as CD in children.

The purpose of this study is to provide an estimate of the national prevalence of CD defined using DSM-IV criteria and to test the hypothesis that exposures to environmental tobacco smoke and childhood lead exposure were associated with CD in a large nationally representative sample of US children.

## **Methods**

### *Data Source*

The data for this analysis came from the National Health and Nutrition Examination Survey (NHANES), conducted from 2001-2004. The NHANES is a cross-sectional household survey of the non-institutionalized civilian population. The NHANES used a complex, multistage probability sampling design, with over-sampling of adolescents 12-19 years of age, adults 60+ years of age, low income persons, Mexican-Americans, and non-Hispanic blacks. This method of over-sampling allows for more valid and precise estimates to be derived among sub-groups than a simple random sampling methodology would. Details regarding interviews, examination procedures, and sample collection have been described elsewhere (NCHS 2007).

### *Assessment of Conduct Disorder*

The National Institute of Mental Health Diagnostic Interview Schedule for Children-Caregiver Module (NIMH DISC) was used to assess for the presence of mental health disorders based on DSM-IV criteria. The DISC is a structured diagnostic interview instrument designed for use by lay interviewers in clinical and epidemiological studies. Reliable versions are available in English and Spanish (Bravo et al. 2001; Shaffer et al. 2000). Caregivers of children age 8 to 15 years completed the CD DISC module in English or Spanish by phone two to four weeks after the child's NHANES Mobile Examination Center (MEC) visit, providing information about the child's CD symptoms over the last 4 weeks, 12 months, and lifetime. DISC algorithms were used to determine whether the child met the criteria for CD diagnosis within the last 4 weeks, 12 months, and lifetime. For the purpose of this analysis, our primary outcomes were meeting DSM-IV CD criteria (dichotomous) and CD symptom count in the last 12 months. Children met DSM-IV CD criteria if they had  $\geq 3$  symptoms in the past 12 months with at least one symptom in the last 6 months. Symptom counts during the past 12 months for children age 8 to 15 years old ranged from 0 to 12 symptoms.

### *Environmental Exposures*

We used parent report to measure children's exposure to tobacco products. Measurement of prenatal tobacco smoke exposure consisted of the question, "Did the child's biological mother smoke at any time while she was pregnant with him/her?" No information on the quantity or brand of cigarettes smoked during pregnancy was collected.

Information on postnatal ETS exposure included parent report about the presence of a smoker in the home, the number of packs of cigarettes smoked in the home, and the child's cotinine levels. Exposure to household ETS was assessed by asking, "Does anyone who lives here smoke cigarettes, cigars, or pipes anywhere inside this home?" In addition, interviewers

asked for the number of cigarettes smoked per day inside the home. Cotinine, a metabolite of nicotine, was measured using high performance liquid chromatography-tandem mass spectrometry (Bernert et al. 2000). The limit of detection (LOD) for this assay was reported to be 0.015 ng/mL; 573 (20.0%) children had levels below this level. Cotinine levels > 10 ng/mL (n=82) are indicative of active smoking, thus children with values above this level were excluded from all analyses (Benowitz et al. 1983).

Blood lead concentration was determined by graphite furnace atomic absorption spectrophotometry (Miller et al. 1987; Parsons and Slavin 1993). The limit of detection was reported to be 0.3 µg/dL: 38 children had blood lead levels below this threshold. We ran secondary analyses excluding children with blood lead levels  $\geq 10$  µg/dL (n=6) to determine whether they had excessive influence on our models.

### Covariates

We examined covariates thought *a priori* to possibly confound the relationship between CD and prenatal tobacco smoke, postnatal ETS, and lead exposure. Demographic variables included the child's age, sex, race, socioeconomic status (as measured by Poverty to Income Ratio [PIR]), and mother's age at child's birth (<18 years vs.  $\geq 18$  years). PIR is the ratio of household income to the poverty threshold for a family of a given size in the respective year of the interview. PIR provides for a better measure of socioeconomic status by controlling for both income and household size. PIR values were coded into four categories to reflect the current standards used in government financed welfare programs (<1.00, 1.00-1.85, 1.85-3.0, and >3.0). Because low birthweight and neonatal intensive care unit (NICU) admission may act as intervening variables on the causal pathway between prenatal tobacco smoke exposure and CD, we did not include these two variables in our multivariate analyses.

### Statistical Analysis

We used logistic regression to analyze the association between environmental, demographic, and medical factors with meeting DSM-IV CD criteria in the past year (yes/no). Poisson regression was used to analyze the association between children's symptom count in the past year and demographic, medical, and environmental factors. Poisson regression models were used to compare the ratio of symptom counts across demographic, medical, and environmental variables along with respective mean symptom counts within strata of these variables. We did not use an offset term in our Poisson models.

Because cotinine provides a more objective measure of ETS exposure than parent report, we used it in our primary analyses. Serum cotinine and blood lead levels were categorized into quintiles and quartiles, respectively, using weighted percents. We also calculated the sensitivity and specificity of parent report of ETS compared to child's cotinine level to determine the proportion of children misclassified as unexposed using parent report of ETS exposure.

We conducted a secondary analysis to determine the effect of postnatal ETS exposure among children without prenatal tobacco smoke exposure. To provide more precise estimates of the effect we only conducted this analysis using CD symptoms counts (Poisson models).

Logistic regression models were used to calculate the odds of meeting DSM-IV CD criteria within each quintile of cotinine exposure or quartile of lead exposure using the 1<sup>st</sup> quintile or quartile as the common referent group. Poisson regression models were fit with the same quintile and quartile categorical variables that were used in logistic regression models.

Regression diagnostics were conducted to identify influential observations, overdispersion, or collinearity. No collinearity or overdispersion was observed. Potential influential observations were identified in the logistic regression models (n=4) and Poisson

regression models (n=20) using dfbetas and studentized residuals, respectively. The exclusion of these outliers did not appreciably alter the estimates of prenatal tobacco smoke exposure, postnatal ETS exposure, or blood lead levels. All multivariable results are reported with influential observations.

Analyses were performed using the SUDAAN statistical package to account for the multi-stage, complex sampling design (RTI 2004). Sample weights were applied according to the NCHS guidelines to produce accurate national estimates, adjusting for the over-sampling of minorities and young children.

This study was approved by the National Center for Health Statistics Institutional Review Board (IRB) and the University of North Carolina-Chapel Hill IRB. Informed consent was obtained from all participants (NCHS 2007).

## **Results**

A total of 3,907 children age 8 to 15 years old were interviewed and 3,799 (97.2%) of these children completed the MEC examination in 2001-2004. A total of 3,081 (78.9%) parents completed the DISC telephone interview and 2,619 (67.0%) children had complete data available for multivariable analysis. Table 1 compares the characteristics of children whose parents did and did not complete the DISC telephone interview. Children whose parents completed the DISC were more likely to be older (13-15 years old), white, in the highest PIR category, have lower blood lead levels, not live with a smoker and have a birthweight >2500 grams compared to the 826 (21.1%) children whose parents did not complete the DISC.

Of the 3,081 children age 8 to 15 years old available for analysis, n=68, or 2.06% (95% CI: 1.47, 2.88), met the DSM-IV criteria for CD in the past year, equivalent to 560,000 US children and adolescents. Children exposed to prenatal tobacco smoke, postnatal ETS, and

environmental lead had a higher prevalence of CD. CD prevalence was higher among male children (2.24%; 95% CI: 1.66%, 3.02%) than female children (1.86%; 95% CI: 1.11, 3.12). The prevalence of CD was also higher among older children (13-15 years of age) than children under age 13 years.

The mean CD symptom count (Table 2) for all US children age 8 to 15 years old was 0.60 (95% CI: 0.54, 0.67). Children who met DSM-IV criteria for CD had, on average, 6.26 (95% CI: 5.70, 6.83) symptoms in the past year, while children without CD had 0.49 (95% CI: 0.44, 0.53) symptoms. Mean symptom counts were higher among male children, older children, and those exposed to environmental toxicants (Table 2).

Among children with cotinine levels  $\leq 10$  ng/mL, 79.1% had detectable cotinine levels. Prenatal tobacco smoke exposure was moderately correlated with the presence of a smoker in the home and the number of cigarettes smoked in the home (Spearman rank  $r = 0.36-0.38$ ). Serum cotinine levels were moderately correlated (Spearman rank  $r = 0.31$ ) with prenatal tobacco smoke exposure and highly correlated with self reported tobacco exposures (Spearman rank  $r = 0.60$ ). Using detectable cotinine levels as the gold standard, 100% (specificity) of children with detectable cotinine levels lived with a smoker in the home. Among children whose parents did not report a smoker in the home, 74.0% (1-sensitivity/false negatives) had detectable cotinine levels.

In multivariable analyses, both prenatal and postnatal exposure to tobacco smoke and children's blood lead levels were significantly associated with meeting DSM-IV criteria for CD when adjusted for covariates (Table 3). Children exposed to prenatal tobacco smoke had a 3.00-fold higher odds of CD than non-exposed children (95% CI: 1.36, 6.63). An increase in blood lead levels (4<sup>th</sup> vs. 1<sup>st</sup> quartile) was associated with an 8.64-fold (95% CI: 1.87, 40.04) increased

odds of meeting DSM-IV CD criteria. Children with serum cotinine levels in the 5<sup>th</sup> quintile had a 9.15-fold (95% CI: 1.47, 56.90) increased odds of meeting DSM-IV CD criteria compared to children with serum cotinine levels below the LOD (0.015 ng/mL).

Poisson regression models showed that exposure to tobacco smoke and children's blood lead concentrations were associated with increased number of CD symptoms among children. Children with prenatal tobacco smoke exposure had 1.68 (95% CI: 1.14, 2.48) times as many CD symptoms as unexposed children (Table 4). Children with higher serum cotinine levels showed an increasing number of CD symptoms compared to children with non-detectable cotinine levels. Children with higher blood lead levels also showed an elevated number of CD symptoms compared with children in the lowest blood lead quartile.

Figure 1 shows the mean number of symptoms among children without any prenatal tobacco smoke exposure. Children with serum cotinine levels in the 5<sup>th</sup> quintile had 2.23-times (95% CI: 1.21, 4.11) as many symptoms as children in the 1<sup>st</sup> quintile of cotinine exposure. The exclusion of children with blood lead levels  $\geq 10$   $\mu\text{g}/\text{dL}$  did not substantially alter the effect estimates of environmental lead exposure in either our logistic or Poisson regression models.

## **Conclusions**

Overall, 2.06% of children surveyed met DSM-IV criteria for CD in the past 12 months, equivalent to 560,000 US children age 8 to 15 years old. This estimate, which is consistent with previous prevalence estimates that range from less than 1.0% to 16.0%, (Lahey et al. 2000; Loeber et al. 2000; Maughan et al. 2004) is the first national estimate of the prevalence of CD in children using DSM-IV criteria. Our analyses confirm prior observations that prenatal tobacco smoke exposure is associated with disruptive behavior disorders in children. We also found increases in the number of CD symptoms among children exposed to postnatal ETS. Finally, we

found that lead exposure, measured using blood lead levels, was associated with increased odds of CD and increased CD symptom count in the past year.

Our results are the first to use a DSM-IV based instrument to assess for conduct problems in a nationally representative sample of US children. Previous work evaluated small to moderately sized case-control sets or prospective cohorts using behavior scales like the CBCL, (Needleman et al. 1996; Wasserman et al. 2001) self/parent-report of delinquent behavior (Dietrich et al. 2001; Needleman et al. 1996), or adjudicated case status (Needleman et al. 2002). Estimates of the prevalence of CD may differ across studies because of diagnostic instrument, informant, time period for assessing psychiatric status, and source population. As noted by Lahey et al., small changes in the diagnostic instrument can produce large changes in the prevalence (Lahey et al. 1999). Using DSM-III R criteria the prevalence of CD in 3 US based samples ranged from 1.2% to 16.0% depending on the age and sex of the children. Using DSM-IV criteria, the prevalence of CD has been reported to be 1.3% for girls and 3.9% for boys (Loeber et al. 2000). We did not find differences in the prevalence of CD diagnosis between boys (2.24%) and girls (1.86%) to be as large as previously reported (Loeber et al. 2000). This may be a result of using parents as the informants of CD symptoms.

In this sample, children with prenatal tobacco smoke exposure had elevated odds of meeting DSM-IV CD criteria, which is consistent with previous reports (Fergusson et al. 1998; Wakschlag et al. 1997; Weissman et al. 1999). Using DSM-IV criteria, Fergusson et al. reported a 1.4 to 2.5 fold increase in CD symptom rate among children whose mothers smoked > 1 pack of cigarettes per day during pregnancy, (Fergusson et al. 1998) which is consistent with the increase in CD symptoms we observed among children exposed to prenatal tobacco smoke. However, unlike our study, Fergusson et al. did not find an association between maternal

smoking during pregnancy and CD diagnosis after controlling for confounding. The difference in our results may be due to differences in the confounders that were controlled for (Fergusson et al. 1998). Fergusson et al. controlled for illicit drug and alcohol use during pregnancy, child-rearing practices, and family functioning. Our reported effect estimates may have been attenuated had we been able to adjust for these other confounders.

Children with increasing cotinine levels had increased odds of meeting DSM-IV CD criteria and an increased prevalence of CD symptoms. This association was not a result of increased serum cotinine levels among actively smoking children since we excluded all children with serum cotinine levels indicative of active smoking ( $\geq 10$  ng/mL). Our result is consistent with previous prospective cohort studies that have found similar increases in behavior problems (Weitzman et al. 1992) and CD (Fergusson et al. 1993) associated with postnatal ETS exposure. Fergusson et al. reported that postnatal ETS exposure was associated with increased CD symptoms at 8, 10, and 12 years of age, using parent informants (Fergusson et al. 1998). Weitzman et al. reported increased scores on the Behavior Problem Index of the A-CBC among children whose mothers smoked only after pregnancy (Weitzman et al. 1992). Our study is the first to use an objective biomarker of tobacco smoke exposure to examine the association between postnatal ETS exposure and severe behavior problems among children.

Serum cotinine levels provide a more accurate assessment of ETS exposure than parent report given the substantial proportion (74.0%; sensitivity=26.0%) of children misclassified as unexposed to tobacco smoke when using parent report of the presence of a smoker in the home. The higher proportion of children classified as exposed using cotinine levels may reflect other tobacco smoke exposures that children encounter outside the home. Previous studies have reported sensitivities in the range of 70-80%, (Boyaci et al. 2006; Cornelius et al. 2003). The

discrepancy in sensitivities is likely a result of previous studies using less sensitive cotinine assays and different methods of obtaining parent-report of tobacco smoke exposures than those used by the NHANES. Our results are consistent with previous reports that show tobacco smoke exposures outside of the home contribute substantially to the variability in children's second hand tobacco smoke exposure. Future studies would be well advised to use cotinine as a measure of ETS exposure in children given the high likelihood of exposure misclassification. Children with blood lead levels  $\geq 1.5$   $\mu\text{g}/\text{dL}$  had a 8.64-fold increased odds of having met DSM-IV CD criteria in the past year compared to children with levels from 0.2 to 0.7  $\mu\text{g}/\text{dL}$ . Our findings, which are consistent with prior research showing an increased risk of delinquency and criminality among children with higher bone or blood lead levels, (Dietrich et al. 2001; Needleman et al. 2002; Needleman et al. 1996; Wasserman et al. 2001) provide evidence that contemporary children with considerably lower levels of lead exposure than those in previous studies remain at increased risk for CD. It should be noted, however, that the results of our logistic regression models were very imprecise due to the small number of cases.

The relationship between environmental toxicant exposure and disruptive behavior disorders is not surprising given the wealth of animal literature showing adverse effects of nicotine and lead exposure on behavior (Ernst et al. 2001; Lidsky and Schneider 2003). It has been hypothesized that tobacco smoke exposure elicits its neurotoxic effects through two mechanisms: 1) fetal hypoxia as a result of carbon monoxide exposure and 2) the direct interaction of nicotine with the developing brain (Wakschlag et al. 2002). Exposure to lead has been observed to cause changes in neurotransmitter concentrations and neurotransmitter receptor density (Lidsky and Schneider 2003). Nicotine interacts with nicotinic acetylcholine receptors, which are present in the developing fetal brain. These receptors are involved in the modulation

of neurotransmitters such as dopamine, serotonin, and  $\gamma$ -amino butyric acid. Thus, prenatal nicotine exposure may produce secondary effects through these other systems (Ernst et al. 2001). Slotkin proposed that nicotine exposure is associated with regional abnormalities in cell number and macromolecule content in rats. In addition, he found that prenatal exposure to nicotine results in a premature switch from cell replication to cell differentiation (Slotkin et al. 1987). Animal models using rats and rhesus monkeys have shown that lead exposed animals exhibit deficits in discrimination reversal, spatial delayed alternation, and fixed interval tasks (Rice 1996; Rice 2000). These deficits indicate impairment in the animals' ability to inhibit inappropriate responses, temporally organize behavior, and learn from the consequences of previous actions. Recent work by Nigg et al. among children with ADHD suggests that behavioural problems may be mediated by child IQ or poor cognitive control (Nigg et al. 2008).

This study has several limitations that should be considered when interpreting our results. First, the cross-sectional nature of the data makes it difficult to infer causal relationships. The results of our study are consistent with previous birth cohorts that prospectively collected exposure information (Dietrich et al. 2001; Fergusson et al. 1998; Weitzman et al. 1992). Concurrent blood lead levels may not be the optimal biomarker of a child's risk for lead-associated behavior problems if lead induces neurotoxic effects during early development. However, recent studies indicate that concurrent blood lead level is a stronger predictor of lead-associated IQ decrements and behavior problems than blood lead measured during early childhood (Chen et al. 2007; Chen et al. 2005; Lanphear et al. 2005). Another potential source of bias in cross-sectional data is exposure misclassification. Mothers of children with behavior problems may be more likely to recall gestational intake of potentially harmful substances, such as tobacco, owing to a drive to identify a cause of their child's disorder. On the other hand,

mothers may fail to report prenatal and postnatal tobacco smoke exposure due to social stigma (i.e., social desirability bias) or tobacco smoke exposures outside of the home. We minimized the possibility that postnatal ETS exposures were misclassified by using cotinine as a marker of exposure. Prior research indicates that mothers can accurately recall gestation intake of tobacco with sensitivities and specificities in the range of 0.81-0.86 and 0.94-0.97, respectively (Jacobson et al. 2002; Tomeo et al. 1999).

Another limitation to the NHANES data is that prenatal tobacco smoke exposure was only collected as a dichotomous variable and we were unable to examine its relationship with CD in more than two categories. This would result in our effect estimate being biased towards the null if the effect of prenatal tobacco smoke exposure on CD diagnosis is greater at higher levels of prenatal tobacco consumption.

Although we were able to adjust for some confounders, we were unable to adjust for maternal education, family functioning, caregiving environment, parenting practices, prenatal alcohol use, and parental psychopathology. These factors tend to be associated with greater exposure to environmental toxicants and greater risk for CD. The NHANES does collect data on maternal education and prenatal alcohol use, but these data were not available in the public use NHANES data files. We did attempt to control for as many confounders (or their proxies) in the relationship between environmental toxicants and CD including race/ethnicity, maternal age at child's birth, and socioeconomic status (PIR). Still, it is unlikely that these confounders would have been strong enough to eliminate our observed associations given the previous literature showing robust effects even after controlling for numerous confounders.

Finally, the small number of exposed cases in our logistic regression model created imprecise estimates of the effect of lead exposure and limited our ability to adequately assess for

an interaction between prenatal tobacco smoke exposure and blood lead levels. Still, the consistency of our results using the CD symptom counts suggests that exposure to environmental toxins may result in a shift of the symptom count distribution that would result in an increased number of CD diagnosed children.

The reported prevalence of CD may be an underestimate of the true national prevalence because we relied on parents as the informants of CD symptoms (Loeber et al. 2000; Shaffer et al. 2000). Many disruptive or delinquent behaviors in children are not recognized by their parents. Although maternal and child report of CD symptoms are correlated, (Burt et al. 2005) some studies found that child informants were twice as likely to meet the diagnostic criteria for CD compared to parent or caregiver informants (Ezpeleta et al. 1997).

This study confirms the previously observed associations between prenatal tobacco smoke exposure and CD. In addition, this study provides support that elevated blood lead levels are a risk factor for CD. Future research should be directed at confirming this observation in prospective birth cohorts, preferably using serial biomarkers of prenatal tobacco smoke exposure and environmental lead exposure. Despite dramatic reductions in children's exposures to tobacco smoke and environmental lead, these results suggest that millions of contemporary children may be exposed to levels of these toxicants sufficient to increase the risk for persistent, disruptive, and even violent behavior problems.

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## Tables

Table 1: Demographic, environmental, and medical factors by DISC response status.

Variable	All children N=3907 (%)	Children With DISC N=3081 (%)	Children without DISC N=826 (%)
<b>Age (in years)</b>			
8-10	1129 (28.9)	861 (27.9)	268 (32.5)
11-12	982 (25.1)	774 (25.1)	208 (25.1)
13-15	1796 (46.0)	1446 (46.9)	350 (42.4)
Missing/Refused	0	0	0
<b>Sex</b>			
Male	1917 (49.1)	1512 (49.1)	405 (49.2)
Female	1990 (50.9)	1569 (50.9)	421 (50.8)
Missing/Refused	0	0	0
<b>Race</b>			
Mexican	1154 (29.5)	928 (30.1)	226 (27.4)
Other Hispanic	150 (3.8)	115 (3.7)	35 (4.3)
White	1109 (28.4)	905 (29.4)	204 (24.8)
Black	1331 (34.1)	1026 (33.3)	305 (36.8)
Other	163 (4.2)	107 (3.5)	56 (6.8)
Missing/Refused	0	0	0
<b>Income to poverty ratio</b>			
<1.00	1151 (31.1)	875 (29.5)	276 (37.2)
1.00-1.85	892 (24.1)	712 (24.0)	180 (24.3)
1.85-3.00	699 (18.9)	571 (19.3)	128 (17.3)
>3.00	964 (26.0)	806 (27.2)	158 (21.2)
Missing/Refused	201	117	84
<b>Prenatal tobacco exposure</b>			
No	3258 (84.4)	2576 (84.6)	682 (82.6)
Yes	601 (15.6)	470 (15.4)	131 (15.9)
Missing/Refused	48	35	13
<b>Does anyone smoke in the home</b>			
No	3007 (78.0)	2420 (79.2)	587 (73.2)
Yes	849 (22.0)	634 (20.8)	215 (26.8)
Missing/Refused	51	27	24
<b>Cotinine Level</b>			
1 <sup>st</sup> quintile (<0.015 ng/mL)	573 (17.5)	509 (18.5)	64 (12.1)
2 <sup>nd</sup> quintile (0.015 to 0.037 ng/mL)	673 (20.5)	583 (21.3)	90 (16.9)
3 <sup>rd</sup> quintile (0.038 to 0.126 ng/mL)	664 (20.3)	568 (20.7)	96 (16.3)
4 <sup>th</sup> quintile (0.127 to 0.673 ng/mL)	766 (23.4)	622 (22.7)	144 (25.0)
5 <sup>th</sup> quintile (0.674 to 9.9 ng/mL)	601 (18.3)	464 (16.8)	137 (29.7)
Active smokers (>10 ng/mL)	82	64	16
Missing/Refused	548	272	276
<b>Blood Lead Quartiles</b>			

1 <sup>st</sup> quartile (0.2 to 0.7 µg/dl)	746 (22.8)	655 (22.9)	91 (16.3)
2 <sup>nd</sup> quartile (0.8 to 1.0 µg/dl)	800 (23.4)	684 (23.9)	116 (20.7)
3 <sup>rd</sup> quartile (1.1 to 1.4 µg/dl)	746 (21.8)	630 (22.0)	116 (20.7)
4 <sup>th</sup> quartile (> 1.5 µg/dl)	1135 (33.0)	898 (31.2)	238 (42.3)
Missing/Refused	480	215	265
Maternal age at birth			
> 18 years	3463 (88.6)	2738 (88.9)	725 (87.8)
≤ 18 years	444 (11.4)	343 (11.1)	101 (12.2)
Missing/Refused	0	0	0
NICU Admission			
No	3393 (87.7)	2682 (88.8)	711 (86.1)
Yes	476 (12.3)	372 (12.2)	104 (12.6)
Missing/Refused	38	27	11
Low birth weight			
≥ 2500 gm	3500 (90.9)	2777 (91.3)	723 (89.6)
<2500 gm	350 (9.1)	266 (8.7)	84 (10.4)
Missing/Refused	57	38	19

Table 2: Prevalence CD<sup>a</sup> and mean DISC symptom count among US children 8-15 years of age according to sociodemographic characteristics, medical, and environmental factors

Variable	Cases	Total	Weighted Percent with DSM-IV Diagnosed CD in the Past 12 Months (95% CI)	Mean Symptom Count in Past Year (95% CI)
Total	68	3082	2.06 (1.47, 2.88)	0.60 (0.54, 0.67)
Age (in years)				
8-10	20	862	1.74 (0.99, 3.03)	0.50 (0.41, 0.59)
11-12	16	774	1.43 (0.67, 3.04)	0.51 (0.36, 0.66)
13-15	32	1446	2.75 (1.71, 4.40)	0.76 (0.64, 0.88)
Sex				
Male	37	1513	2.24 (1.66, 3.02)	0.70 (0.65, 0.75)
Female	31	1569	1.86 (1.11, 3.12)	0.50 (0.39, 0.61)
Race				
Mexican	11	928	1.36 (0.62, 2.96)	0.47 (0.39, 0.54)
Other Hispanic	3	115	2.68 (0.56, 11.83)	0.43 (0.15, 0.71)
White	19	906	1.94 (1.18, 3.19)	0.59 (0.50, 0.68)
Black	31	1026	2.98 (1.76, 4.99)	0.89 (0.77, 1.00)
Other	4	107	1.75 (0.54, 5.52)	0.49 (0.24, 0.74)
Income to poverty ratio				
<1.00	25	875	2.35 (1.22, 4.47)	0.78 (0.65, 0.91)
1.00-1.85	21	712	3.19 (1.52, 6.58)	0.69 (0.53, 0.85)
1.85-3.00	8	571	2.10 (0.92, 4.70)	0.59 (0.44, 0.73)
>3.00	11	807	1.21 (0.56, 2.58)	0.47 (0.37, 0.57)
Prenatal tobacco exposure				
No	40	2577	1.16 (0.79, 1.69)	0.48 (0.42, 0.55)
Yes	25	470	5.36 (2.98, 9.46)	1.09 (0.83, 1.35)
Does anyone smoke in the home				
No	38	2421	1.43 (0.91, 2.26)	0.50 (0.44, 0.57)
Yes	28	634	4.19 (2.36, 7.33)	0.95 (0.81, 1.10)
Cotinine Level				
1 <sup>st</sup> quintile (<0.015 ng/mL)	3	509	0.31 (0.09, 1.01)	0.34 (0.24, 0.44)
2 <sup>nd</sup> quintile (0.015 to 0.037 ng/mL)	4	582	0.70 (0.18, 2.64)	0.31 (0.19, 0.43)
3 <sup>rd</sup> quintile (0.038 to 0.126 ng/mL)	9	568	1.09 (0.40, 2.94)	0.54 (0.42, 0.66)
4 <sup>th</sup> quintile (0.127 to 0.673 ng/mL)	17	622	4.00 (1.65, 9.35)	0.77 (0.59, 0.95)
5 <sup>th</sup> quintile (0.674 to 9.9 ng/mL)	26	464	5.15 (2.72, 9.52)	1.10 (0.89, 1.31)
Blood Lead Quartiles				
1 <sup>st</sup> quartile (0.2 to 0.7 µg/dl)	4	655	0.32 (0.09, 1.06)	0.36 (0.28, 0.44)
2 <sup>nd</sup> quartile (0.8 to 1.0 µg/dl)	11	684	1.88 (0.94, 3.71)	0.60 (0.47, 0.74)
3 <sup>rd</sup> quartile (1.1 to 1.4 µg/dl)	22	630	4.06 (0.94, 3.71)	0.70 (0.53, 0.86)
4 <sup>th</sup> quartile (≥ 1.5 µg/dl)	29	898	3.02 (1.96, 4.63)	0.85 (0.74, 0.97)
Maternal age at birth of child				
> 18 years	54	2739	1.92 (1.30, 2.82)	0.58 (0.51, 0.65)
≤ 18 years	14	343	4.02 (1.97, 8.03)	0.98 (0.72, 1.24)
NICU admission				

No	51	2683	1.75 (1.13, 2.70)	0.57 (0.50, 0.65)
Yes	12	372	3.88 (1.98, 7.47)	0.77 (0.57, 0.97)
Low birth weight				
≥ 2500 gm	57	2778	1.88 (1.25, 2.80)	0.59 (0.52, 0.66)
<2500 gm	9	266	4.26 (1.70, 10.24)	0.77 (0.50, 1.04)

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a-Diagnosed according to DSM-IV criteria using the DISC Caregiver Module

Table 3: Adjusted OR for meeting DSM-IV CD diagnosis criteria in the past year among US children 8 to 15 years of age<sup>a</sup>

Variable	Cases	Total	Adjusted OR for Meeting DSM-IV CD Criteria (95% CI)
Age (in years)	68	862	1.08 (0.88, 1.31)
Sex			
Female	31	1569	Ref
Male	37	1513	1.00 (0.55, 1.80)
Income to poverty ratio (PIR)			
>3.00	11	807	Ref
<1.00	25	875	0.84 (0.26, 5.83)
1.00-1.85	21	712	1.24 (0.26, 5.83)
1.85-3.00	8	571	1.26 (0.46, 3.52)
Race			
White	19	906	Ref
Mexican	11	928	1.01 (0.24, 4.27)
Other Hispanic	3	115	0.98 (0.14, 7.03)
Black	31	1026	1.06 (0.42, 2.70)
Other	4	107	1.14 (0.27, 4.79)
Maternal age at birth of child			
> 18 years	54	2739	Ref
≤ 18 years	14	343	1.30 (0.44, 3.87)
Prenatal Tobacco Exposure			
No	40	2577	Ref
Yes	25	470	3.00 (1.36, 6.63)
Cotinine Level			
1 <sup>st</sup> quintile (<0.015 ng/mL)	3	509	Ref
2 <sup>nd</sup> quintile (0.015 to 0.037 ng/mL)	4	582	1.00 (0.15, 6.91)
3 <sup>rd</sup> quintile (0.038 to 0.126 ng/mL)	9	568	2.84 (0.46, 17.42)
4 <sup>th</sup> quintile (0.127 to 0.673 ng/mL)	17	622	10.22 (1.70, 61.40)
5 <sup>th</sup> quintile (0.674 to 9.9 ng/mL)	26	464	9.15 (1.47, 56.90)
Blood Lead Quartiles			
1 <sup>st</sup> quartile (0.2 to 0.7 µg/dl)	4	655	Ref
2 <sup>nd</sup> quartile (0.8 to 1.0 µg/dl)	11	684	7.24 (1.06, 49.47)
3 <sup>rd</sup> quartile (1.1 to 1.4 µg/dl)	22	630	12.37 (2.37, 64.56)
4 <sup>th</sup> quartile (1.5 to 10.0 µg/dl)	29	898	8.64 (1.87, 40.04)

a-Adjusted for child's age in years, PIR, maternal age at child's birth, child's sex, child's race, prenatal tobacco smoke exposure, cotinine levels, and blood lead levels.

Table 4: Poisson regression analysis for CD symptom count in the past year among US children 8 to 15 years of age<sup>a</sup>

Variable	Cases	Total	Adjusted Symptom Ratio <sup>b</sup> (95% CI)
Age (in years)	68	862	1.08 (1.02, 1.15)
Sex			
Female	31	1569	Ref
Male	37	1513	1.37 (1.06, 1.75)
Income to poverty ratio			
>3.00	11	807	Ref
<1.00	25	875	1.09 (0.77, 1.54)
1.00-1.85	21	712	1.09 (0.67, 1.80)
1.85-3.00	8	571	1.11 (0.85, 1.44)
Race			
White	19	906	Ref
Mexican	11	928	0.88 (0.67, 1.16)
Other Hispanic	3	115	0.74 (0.38, 1.45)
Black	31	1026	1.22 (0.95, 1.56)
Other	4	107	1.03 (0.63, 1.67)
Maternal age at birth of child			
> 18 years	54	2739	Ref
≤ 18 years	14	343	1.19 (0.80, 1.77)
Prenatal Tobacco Exposure			
No	40	2577	Ref
Yes	25	470	1.68 (1.14, 2.48)
Cotinine Level			
1 <sup>st</sup> quintile (<0.015 ng/mL)	3	509	Ref
2 <sup>nd</sup> quintile (0.015 to 0.037 ng/mL)	4	582	0.74 (0.38, 1.45)
3 <sup>rd</sup> quintile (0.038 to 0.126 ng/mL)	9	568	1.31 (0.93, 1.85)
4 <sup>th</sup> quintile (0.127 to 0.673 ng/mL)	17	622	1.61 (1.04, 2.48)
5 <sup>th</sup> quintile (0.674 to 9.9 ng/mL)	26	464	1.97 (1.15, 3.40)
Blood Lead Quartiles			
1 <sup>st</sup> quartile (0.2 to 0.7 µg/dl)	4	655	Ref
2 <sup>nd</sup> quartile (0.8 to 1.0 µg/dl)	11	684	1.55 (1.09, 2.22)
3 <sup>rd</sup> quartile (1.1 to 1.4 µg/dl)	22	630	1.50 (1.04, 2.17)
4 <sup>th</sup> quartile (1.5 to 10.0 µg/dl)	29	898	1.73 (1.23, 2.43)

a-Adjusted for child’s age in years, PIR, maternal age at child’s birth, child’s sex, child’s race, prenatal tobacco smoke exposure, cotinine levels, and blood lead levels.

b-The symptom ratio is the increase in the symptom rate in the index category compared to the referent category.

Figure 1: Adjusted mean symptom CD symptom counts by serum cotinine quintile among children without prenatal tobacco smoke exposure. <sup>a,b</sup>

a- Adjusted for child's age in years, PIR, maternal age at child's birth, child's sex, child's race, prenatal tobacco smoke exposure, and cotinine levels.

b-The mean symptom count is derived from the Poisson regression models presented in Table 4.

c-Error bars represent 95% confidence intervals

Figure 1

