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Association of Tobacco and Lead Exposures With Attention-Deficit/Hyperactivity Disorder



WHAT'S KNOWN ON THIS SUBJECT: Prenatal tobacco and childhood lead exposures have been associated with hyperactivity and inattentive symptoms, but little is known about their independent and potential combined effects on attention-deficit/hyperactivity disorder, as defined with current diagnostic criteria.



WHAT THIS STUDY ADDS: This study is the first to determine the independent effects of tobacco and lead exposures on ADHD in a nationally representative sample of US children using DSM-IV criteria for outcome assessment, and provides the first estimate of the joint effects of these common toxicants on ADHD.

abstract

OBJECTIVE: The study objective was to determine the independent and joint associations of prenatal tobacco and childhood lead exposures with attention-deficit/hyperactivity disorder (ADHD), as defined by current diagnostic criteria, in a national sample of US children.

METHODS: Data are from the 2001–2004 National Health and Nutrition Examination Survey, a cross-sectional, nationally representative sample of the US population. Participants were 8 to 15 years of age ($N = 2588$). Prenatal tobacco exposure was measured by report of maternal cigarette use during pregnancy. Lead exposure was assessed by using current blood lead levels. The Diagnostic Interview Schedule for Children was used to ascertain the presence of ADHD in the past year, on the basis of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria.

RESULTS: A total of 8.7% (95% confidence interval [CI]: 7.3%–10.1%) of children met criteria for ADHD. Prenatal tobacco exposure (adjusted odds ratio [aOR]: 2.4 [95% CI: 1.5–3.7]) and higher current blood lead concentrations (aOR for third versus first tertile: 2.3 [95% CI: 1.5–3.8]) were independently associated with ADHD. Compared with children with neither exposure, children with both exposures (prenatal tobacco exposure and third-tertile lead levels) had an even greater risk of ADHD (aOR: 8.1 [95% CI: 3.5–18.7]) than would be expected if the independent risks were multiplied (tobacco-lead exposure interaction term, $P < .001$).

CONCLUSIONS: Prenatal tobacco and childhood lead exposures are associated with ADHD in US children, especially among those with both exposures. Reduction of these common toxicant exposures may be an important avenue for ADHD prevention. *Pediatrics* 2009;124:e1054–e1063

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KEY WORDS

attention-deficit/hyperactivity disorder, lead exposure, tobacco exposure, toxicant interactions, joint effects

ABBREVIATIONS

ADHD—attention-deficit/hyperactivity disorder
CI—confidence interval
aOR—adjusted odds ratio
DSM-IV—*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
NHANES—National Health and Nutrition Examination Survey
DISC—Diagnostic Interview Schedule for Children
PAF—population attributable fraction

Data analyzed for this investigation were collected by the National Center for Health Statistics. All analyses, interpretations, and conclusions expressed in this article are those of the authors and not the National Center for Health Statistics, which is responsible only for the initial data.

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Attention-deficit/hyperactivity disorder (ADHD), one of the most common childhood neurobehavioral conditions, is characterized by developmentally inappropriate difficulties sustaining attention, controlling impulses, and modulating activity levels. It is associated with substantial health care costs¹ and impaired social, academic, and occupational functioning.^{2,3} Although ADHD is thought to be a highly familial disorder,⁴ environmental factors also have been implicated.^{5,6} Many, but not all, previous studies documented an association between prenatal tobacco exposure and attention problems.^{5,7–10} Lead exposure also has been linked to inattention and impulsivity,^{11,12} although most previous studies enrolled children with lead levels higher than those that are typical today.^{11–15} Few previous studies documented the relationship between ADHD, defined on the basis of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), criteria, and prenatal tobacco exposure^{10,16–18} or childhood lead exposure,^{19,20} and none used nationally representative samples. Furthermore, studies examining joint effects of lead and tobacco are lacking, despite calls to evaluate the combined effects of environmental exposures^{21–23} on ADHD.²⁴ Because both lead and prenatal tobacco exposures alter dopamine systems,^{25–28} the combination of these toxicants may be especially relevant to ADHD pathogenesis. The purpose of this study was to determine the independent and joint effects of tobacco and lead exposures on DSM-IV–defined ADHD in a national sample of US children.

METHODS

Sample

The National Health and Nutrition Examination Survey (NHANES) is a multi-stage, probability sample survey of the

US population. In 2001–2004, 3907 children 8 to 15 years of age participated in NHANES. Data regarding ADHD DSM-IV diagnostic status were available for 3077 children (78.8% of total), and 2588 children (66.2% of total) had complete data regarding lead exposure, smoke exposure, and additional predictors. Children with and without ADHD DSM-IV data did not differ in terms of gender, prenatal smoke exposure, birth weight, or NICU admission (all $P > .26$). However, children lacking DSM-IV data were significantly more likely to be younger (mean age: 9.9 vs 12.1 years), poorer (lowest income quintile: 24.9% vs 18.9%), and exposed to lead (third tertile of exposure: 40.9% vs 29.2%) and household tobacco smoke (third tertile of exposure: 49.7% vs 31.7%).

Outcomes

Our primary outcome was ADHD, defined on the basis of meeting DSM-IV criteria for any ADHD subtype. The National Institute of Mental Health Diagnostic Interview Schedule for Children (DISC) was used to assess DSM-IV–defined ADHD on the basis of standardized algorithms, as in previous studies.²⁹ The DISC is a structured diagnostic interview instrument designed for use in epidemiological and clinical studies, with reliable versions available in English³⁰ and Spanish.^{31,32} Caregivers completed the ADHD DISC module 2 to 4 weeks after the child's NHANES Mobile Examination Center evaluation, providing information about the child's ADHD symptoms, the age of onset, symptom pervasiveness, and related impairments in the previous 12 months.

To account for children who did not currently meet ADHD DSM-IV criteria because of appropriate medication treatment, we created a secondary outcome variable for which children

were considered to have ADHD if they either demonstrated positive findings on the DISC for any ADHD subtype or had been treated with ADHD medications during the past year and had a caregiver report of a previous ADHD diagnosis. Questions on the DISC inquire about the use of “medicine for being overactive, being hyperactive, or having trouble paying attention” in the past 12 months. To determine whether a child had a previous ADHD diagnosis, caregivers were asked, during a separate NHANES interview module, “Has a doctor or health professional ever told you that [child's name] had attention deficit disorder?”

Primary Predictors

Primary predictors included prenatal tobacco smoke exposure and current lead exposure. Prenatal tobacco exposure was assessed by asking caregivers, “Did the child's biological mother smoke at any time while she was pregnant with him/her?” No information on the quantity of cigarettes smoked was collected. Current blood lead concentrations were determined through graphite furnace atomic absorption spectrophotometry.^{33,34} The limit of detection was 0.3 $\mu\text{g}/\text{dL}$, and 33 children had blood lead levels below this threshold. For primary analyses, lead levels were categorized in tertiles by using weighted percentages, with the first tertile representing the lowest level of exposure and the third tertile the highest. Secondary analyses evaluated the association between ADHD and natural logarithmically transformed lead levels.

Additional Predictors

We examined covariates and potential confounders for the association of prenatal tobacco and current lead exposures with ADHD. Predictors were chosen on the basis of their association with ADHD in previous studies and included child gender,³⁵ household in-

come/poverty line ratio,²⁹ age,³⁵ race/ethnicity,³⁶ mother's age at child's birth,³⁷ birth weight,³⁸ NICU admission,³⁹ postnatal secondhand tobacco smoke exposure,^{40,41} and preschool attendance.⁵ The household income/poverty line ratio, that is, the ratio of the reported household income to the poverty threshold appropriate for the household size, was categorized into quintiles. Child race/ethnicity was designated by caregivers and included the categories of non-Hispanic black, Mexican American, other Hispanic, non-Hispanic white, and other (including multiracial). Because of proportionately small numbers of subjects in the other Hispanic ($n = 114$) and other (including multiracial) ($n = 107$) groups, the groups were combined into a single other race/ethnicity category. Current secondhand tobacco exposure was assessed by using the child's serum levels of cotinine, a metabolite of nicotine. Cotinine levels were measured with high performance liquid chromatography-tandem mass spectrometry.⁴² Cotinine levels of >10 ng/mL ($n = 64$) often are indicative of active smoking, which has been associated with ADHD in adolescent children⁴³; therefore, children with values above this level were excluded from analyses, to prevent confounding of the effects of secondhand tobacco exposure.⁴⁴ In models predicting either fulfillment of ADHD DSM-IV criteria or previous disorder recognition plus ADHD medication treatment, health insurance status was included to account for differing health care access.

Analyses

The Cincinnati Children's Hospital Medical Center institutional review board determined this study to be exempt from review. Descriptive statistics on the national prevalence rates of ADHD (any subtype) are presented for the primary predictors and additional pre-

dictors. Logistic regression analyses were used to analyze the associations between the primary predictors and ADHD status. Additional predictors associated with ADHD (χ^2 test, $P < .2$) in bivariate analyses were included in the logistic regression analyses. In addition, secondary analyses excluded children with lead levels of ≥ 5 $\mu\text{g}/\text{dL}$ ($n = 51$), to determine whether they had excessive influence on the models.

After developing the multivariate main effects model, we tested for joint toxicant effects. We first modeled the potential prenatal tobacco-lead exposure interaction by using a variable with 6 categories, as recommended by Rothman,⁴⁵ that is, no prenatal tobacco exposure and lead levels in the first tertile (reference category), no prenatal tobacco exposure and lead levels in the second tertile, no prenatal tobacco exposure and lead levels in the third tertile, prenatal tobacco exposure and lead levels in the first tertile, prenatal tobacco exposure and lead levels in the second tertile, and prenatal tobacco exposure and lead levels in the third tertile. We also tested whether the formal prenatal tobacco-lead exposure interaction term was statistically significant.

We calculated population attributable fractions (PAFs) of ADHD for lead and prenatal tobacco exposures by using the Miettinen formula.⁴⁶ Because these independent risk factors are not mutually exclusive, we also estimated the PAFs for children with prenatal tobacco exposure, childhood lead exposure, or both.

Regression diagnostic analyses were conducted to identify collinearity and influential observations. No evidence of collinearity was identified (all condition indices were <12). Influential observations were excluded from analyses for assessment of whether their inclusion altered results ($n = 3$). Exclusion of outliers did not influence

significantly the estimates for prenatal tobacco or current lead exposure. Therefore, findings for the full sample, including outliers, are reported.

Because of the complex differential probabilities of selection to achieve oversampling of selected groups in the NHANES cohort, sample weights were applied according to National Center for Health Statistics guidelines for generation of all estimates. Analyses were performed by using SUDAAN 9 (Research Triangle Institute, Research Triangle Park, NC) procedures for analysis of complex surveys.

RESULTS

Main Effects of Environmental and Sociodemographic Factors

Among 8- to 15-year-old participants, 8.7% (95% confidence interval [CI]: 7.3%–10.1%) met DSM-IV–defined ADHD criteria in the year before the survey, equivalent to 2.4 million children in the United States, as reported in our previous study.²⁹ In bivariate analyses, ADHD rates were higher for children with prenatal tobacco exposure ($P < .001$), increasing lead exposure ($P < .001$), current household tobacco exposure (assessed through serum cotinine levels; $P = .01$), male gender ($P < .001$), and a history of attending preschool ($P = .01$) (Table 1).

In multivariate models, prenatal tobacco exposure and current blood lead concentrations were significant predictors of DSM-IV–defined ADHD (Table 2 and Fig 1). Children who were exposed to tobacco prenatally were more than twice as likely to meet ADHD criteria, compared with children who were not exposed (adjusted odds ratio [aOR]: 2.4 [95% CI: 1.5–3.7]). Compared with children in the lowest tertile of lead exposure, those with lead levels in the highest tertile were at significantly higher risk of ADHD (aOR: 2.3 [95% CI: 1.5–3.8]). Current household tobacco exposure was not significantly linked

TABLE 1 Prevalence of ADHD According to Environmental Exposure, Sociodemographic Characteristics, and Medical Factors

| Characteristic | No. With ADHD ^a | Weighted Proportion With ADHD, Estimate (95% CI), % | <i>P</i> ^b |
|---------------------------------------|----------------------------|---|-----------------------|
| Total | 222 | 8.7 (7.3–10.1) | |
| Blood lead level | | | <.001 |
| First tertile (0.2–0.8 μg/dL) | 43 | 5.2 (3.4–7.0) | |
| Second tertile (0.9–1.3 μg/dL) | 63 | 9.1 (5.8–12.5) | |
| Third tertile (>1.3 μg/dL) | 107 | 13.6 (11.0–16.2) | |
| Prenatal tobacco exposure | | | <.001 |
| Yes | 63 | 16.8 (12.3–21.4) | |
| No | 152 | 6.6 (5.2–8.0) | |
| Household smoke exposure ^c | | | .01 |
| First tertile (0.2–0.027 ng/mL) | 47 | 7.0 (4.1–9.9) | |
| Second tertile (0.028–0.202 ng/mL) | 70 | 8.3 (5.5–11.2) | |
| Third tertile (0.203–10 ng/mL) | 88 | 12.4 (9.8–15.1) | |
| Gender | | | <.001 |
| Male | 141 | 11.8 (9.8–13.8) | |
| Female | 81 | 5.4 (4.2–6.6) | |
| Age | | | .08 |
| 8–11 y | 119 | 10.0 (7.9–12.1) | |
| 12–15 y | 103 | 7.5 (5.5–9.4) | |
| Race/ethnicity | | | .06 |
| Mexican American | 45 | 6.0 (4.3–7.8) | |
| Non-Hispanic black | 76 | 8.7 (6.4–10.9) | |
| Other race/ethnicity | 17 | 5.2 (1.8–8.7) | |
| Non-Hispanic white | 84 | 9.8 (7.4–12.1) | |
| Income/poverty ratio | | | .19 |
| First quintile (0–0.93) | 69 | 11.0 (7.9–14.0) | |
| Second quintile (0.94–1.70) | 46 | 9.6 (4.7–14.5) | |
| Third quintile (1.71–2.75) | 40 | 8.5 (4.6–12.5) | |
| Fourth quintile (2.76–4.24) | 34 | 9.0 (5.5–12.6) | |
| Fifth quintile (>4.24) | 28 | 6.4 (3.6–9.1) | |
| Attended preschool | | | .01 |
| Yes | 171 | 9.5 (7.7–11.3) | |
| No | 51 | 6.4 (4.8–8.0) | |
| Mother's age at child's birth | | | .12 |
| ≤18 y | 28 | 13.1 (7.1–19.1) | |
| >18 y | 194 | 8.4 (7.0–9.7) | |
| NICU admission | | | .43 |
| Yes | 32 | 10.2 (6.1–14.2) | |
| No | 186 | 8.4 (6.9–9.9) | |
| Birth weight | | | .18 |
| <2.5 kg | 23 | 14.3 (6.6–21.9) | |
| ≥2.5 kg | 197 | 8.3 (6.6–9.9) | |

^a Subjects with ADHD met DSM-IV criteria for any ADHD subtype.

^b For between-group comparison of prevalence rates in χ^2 analyses.

^c Assessed through serum cotinine levels.

to ADHD in multivariate models (aOR for third versus first tertile of exposure: 0.8 [95% CI: 0.4–1.7]). Multivariate analyses confirmed that children who had attended preschool (aOR: 1.6 [95% CI: 1.1–2.1]) and boys (aOR versus girls: 1.9 [95% CI: 1.4–2.5]) had increased likelihoods of ADHD, whereas Mexican American (aOR: 0.5 [95% CI: 0.3–0.9]) and black (aOR: 0.5 [95% CI: 0.3–0.9]) children had lower likelihoods of ADHD, compared with non-Hispanic white children.

We examined the stability of our results by (1) conducting sensitivity analyses to evaluate effects at lead levels of ≤ 5 μg/dL, (2) determining the relationship of the environmental exposures to DSM-IV–defined ADHD when lead and cotinine levels were modeled as natural logarithmically transformed continuous variables, and (3) expanding the definition of our ADHD outcome. When the sample was restricted to children with lead concentrations of ≤ 5 μg/dL, increasing lead levels were still significantly associated with

DSM-IV–defined ADHD; compared with children in the lowest tertile (nondetectable to 0.8 μg/dL), those with lead levels in the highest tertile (>1.3–5 μg/dL) had a more than twofold increased risk of ADHD (aOR for third versus first tertile: 2.3 [95% CI: 1.4–3.7]). In addition, the observed relationships with DSM-IV–defined ADHD did not change for either lead exposure (aOR: 1.8 [95% CI: 1.2–2.8]) or current household tobacco exposure (aOR: 1.0 [95% CI: 0.9–1.1]) when lead and cotinine levels were treated as natural logarithmically transformed continuous variables. When our outcome was broadened to include either children who currently met DSM-IV criteria for ADHD (8.7% of the sample [95% CI: 7.3%–10.1% of the sample]) or those who did not meet DSM-IV criteria for ADHD but had both a parent-reported previous diagnosis of ADHD and treatment with ADHD medications (3.3% of the sample [95% CI: 2.4%–4.1% of the sample]), both prenatal tobacco exposure (aOR: 2.0 [95% CI: 1.3–3.1]) and current lead exposure (aOR: 2.0 [95% CI: 1.3–3.0]) remained associated with ADHD.

Joint Toxicant Effects

Compared with children with neither exposure, children with both prenatal tobacco exposure and lead levels in the highest tertile had a greater than eightfold increased likelihood of DSM-IV–defined ADHD (aOR: 8.1 [95% CI: 3.5–18.7]) (Fig 2). The formal lead-prenatal tobacco exposure interaction term was statistically significant ($P < .001$), which indicated that the joint effects of exposures operated in a manner that was more than multiplicative. In our sample, children with both prenatal tobacco exposure and current lead concentrations in the highest tertile constituted 7.7% (95% CI: 5.7%–9.8%) of the population but accounted for 24.4% (95% CI: 19.3%–30.5%) of ADHD cases.

TABLE 2 AORs for ADHD According to Environmental Exposure, Sociodemographic Characteristics, and Medical Factors (*N* = 2588)

| Characteristic | AOR (95% CI) | <i>P</i> |
|---|----------------|----------|
| Blood lead level | | |
| First tertile (0.2–0.8 μg/dL) (reference) | 1.0 | |
| Second tertile (0.9–1.3 μg/dL) | 1.7 (0.97–2.9) | .06 |
| Third tertile (>1.3 μg/dL) | 2.3 (1.5–3.8) | .001 |
| Prenatal tobacco exposure | | |
| Yes | 2.4 (1.5–3.7) | .001 |
| No (reference) | 1.0 | |
| Household smoke exposure^a | | |
| First tertile (0.2–0.027 ng/mL) (reference) | 1.0 | |
| Second tertile (0.028–0.202 ng/mL) | 0.9 (0.4–1.7) | .70 |
| Third tertile (0.203–10 ng/mL) | 0.8 (0.4–1.7) | .58 |
| Gender | | |
| Male | 1.9 (1.4–2.5) | <.001 |
| Female (reference) | 1.0 | |
| Age | | |
| 8–11 y | 1.1 (0.8–1.6) | .60 |
| 12–15 y (reference) | 1.0 | |
| Race/ethnicity | | |
| Mexican American | 0.5 (0.3–0.9) | .03 |
| Non-Hispanic black | 0.5 (0.3–0.9) | .02 |
| Other race/ethnicity | 0.4 (0.2–1.1) | .08 |
| Non-Hispanic white (reference) | 1.0 | |
| Income/poverty ratio | | |
| First quintile (0–0.93) | 1.9 (0.9–4.1) | .09 |
| Second quintile (0.94–1.70) | 1.5 (0.7–3.4) | .31 |
| Third quintile (1.71–2.75) | 1.5 (0.8–3.1) | .23 |
| Fourth quintile (2.76–4.24) | 1.4 (0.7–2.6) | .35 |
| Fifth quintile (>4.24) (reference) | 1.0 | |
| Attended preschool | | |
| Yes | 1.6 (1.1–2.1) | .01 |
| No (reference) | 1.0 | |
| Mother's age at child's birth | | |
| ≤18 y | 1.9 (0.96–3.6) | .06 |
| >18 y (reference) | 1.0 | |
| Birth weight | | |
| <2.5 kg | 1.5 (0.7–2.9) | .25 |
| ≥2.5 kg (reference) | 1.0 | |

Subjects with ADHD met DSM-IV criteria for any ADHD subtype.

^a Assessed through serum cotinine levels.

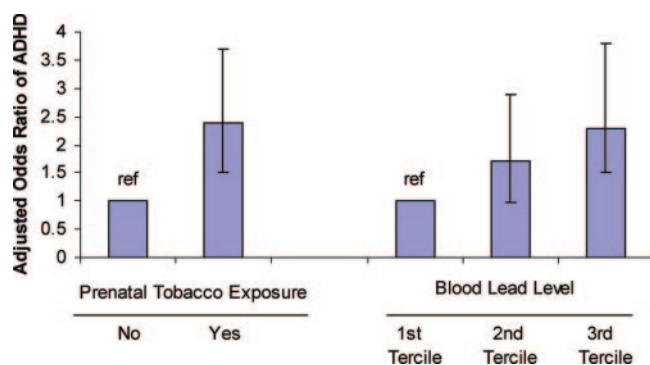


FIGURE 1

AORs for ADHD according to environmental factors. Subjects with ADHD met DSM-IV criteria for any ADHD subtype. ref indicates reference group.

Population Attributable Fractions

We calculated PAFs to estimate the proportion of ADHD cases that might be attributable to prenatal tobacco exposure and current lead exposure if the toxicant exposures were indeed causally linked to ADHD (Table 3). The PAF for prenatal tobacco exposure was 21.7% (95% CI: 12.1%–27.6%), corresponding to 510 000 cases of DSM-IV–defined ADHD in US children 8 to 15 years of age. We also estimated that 25.4% (95% CI: 13.9%–32.5%) of ADHD cases among 8- to 15-year-old children (corresponding to 598 000 cases) might be attributable to lead exposure in the highest tertile. In addition, we calculated the PAF for having ≥1 toxicant exposure. Our estimates suggested that 38.2% (95% CI: 22.5%–47.0%) of ADHD cases among 8- to 15-year-old children might be attributable to prenatal tobacco exposure, lead concentrations of >1.3 μg/dL, or both, corresponding to 900 000 excess cases.

DISCUSSION

Our results suggested that prenatal tobacco and childhood lead exposures were risk factors for ADHD in a nationally representative sample of US children and that the effects of the 2 exposures were even greater than would be expected if their independent effects were multiplied. These findings provide additional support for the association of prenatal tobacco exposure^{6,10,16} and childhood lead exposure^{19,20} with inattention and hyperactivity. In addition, we are the first, to our knowledge, to identify and to quantify the joint effects on ADHD of these common toxicant exposures.

This study had several strengths, including our use of current ADHD diagnostic criteria and a national, population-based sample of children with low-level lead exposures that are relevant for contemporary children.

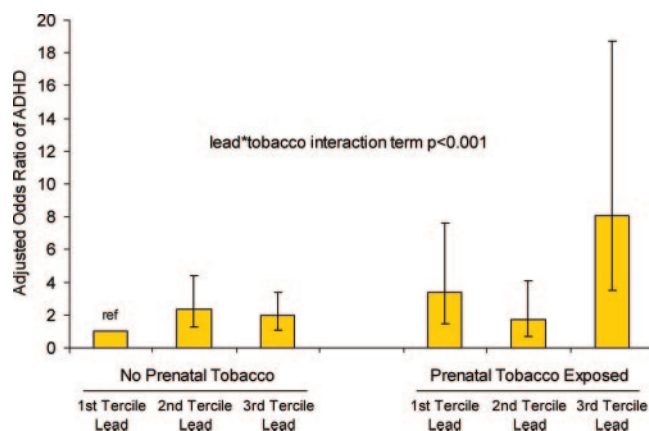


FIGURE 2

Joint effects of prenatal tobacco and current lead exposures on ADHD. Subjects with ADHD met DSM-IV criteria for any ADHD subtype. ref indicates reference group.

Our findings agree with previous smaller studies that documented relationships between DSM-IV–defined ADHD and prenatal tobacco exposure^{10,16} and childhood lead exposure,^{19,20} and our use of a national, population-based sample yields increased generalizability. Evidence of the link between ADHD and the toxicants remained significant even after adjustment for a range of covariates and exclusion of children with current blood lead levels of $>5 \mu\text{g}/\text{dL}$. It is important to note that, although only a small subset of children ($n = 51$) in our sample had current lead levels of $>5 \mu\text{g}/\text{dL}$, it is likely that many more had peak lead concentrations above this level, because longitudinal studies documented peak levels that were 1.9 to 2.8 times greater than levels in later childhood (eg, 5 to 6 years of age).^{47,48}

We documented a significant interaction between prenatal tobacco exposure and childhood lead exposure, such that children with both exposures had a more than eightfold increased likelihood of ADHD, compared with children with neither exposure. This finding adds to the small but growing literature documenting the interactive effects of toxicant exposures on neurodevelopmental outcomes,^{49,50} including previous evidence that hyperactivity was potentiated in animals exposed to both nicotine neonatally and paraoxon during adulthood.⁵¹ The published literature includes extensive documentation of the impact of both tobacco^{27,52} and lead^{25,26} on brain dopamine systems, which provides a plausible locus for their joint effects. Indeed, previous studies showed both lead^{53–56} and tobacco^{16,57–59} effects on dopamine receptors. Additional sites

of action, such as the dopamine transporter,^{60,61} also may play a key role in the toxicants' ADHD-related interaction. The multihit model of neurotoxicity postulates that insults to different targets within a specific brain system compromise homeostatic and repair capacities, thereby increasing the system's vulnerability.²¹

Important limitations to our study must be noted. First, our study cannot verify causality because of its cross-sectional design. It has been postulated that the relationships between the toxicant exposures and ADHD might be explained by unmeasured genetic factors (a propensity to smoke might be associated with maternal ADHD⁴³ that is transmitted genetically to the offspring) or the presence of confounding environmental factors, such as prenatal alcohol exposure.⁸ However, previous investigations that addressed those factors still found significant associations between the toxicants and ADHD, including studies that accounted for genetic influences⁶² and studies that adjusted for both parental psychopathologic conditions and prenatal alcohol use.^{8–10,12,20,63} Moreover, animal studies in which the case and control subjects had identical genetic lineages and differed only in their toxicant exposures documented links between ADHD-related phenotypes and both early tobacco^{64–67} and lead^{68–70} exposures.

In addition, our study is limited in that assessment of prenatal tobacco expo-

TABLE 3 PAFs for Prenatal Tobacco Exposure and Childhood Lead Exposure for ADHD in US Children

| Characteristic | Proportion of Patients With ADHD Exposed, Estimate (95% CI), % | AOR ^a | PAF, Estimate (95% CI), % ^a | Excess Cases ^a |
|--|--|------------------|--|---------------------------|
| Prenatal smoke exposure | 37.7 (31.8–44.2) | 2.4 | 21.7 (12.1–27.6) | 510 000 |
| Blood lead level in third tertile | 44.3 (37.9–50.7) | 2.3 | 25.4 (13.9–32.5) | 598 000 |
| Prenatal smoke exposure and/or blood lead level in third tertile | 58.4 (51.7–64.5) | 2.9 | 38.2 (22.5–47.0) | 900 000 |
| Prenatal smoke exposure and blood lead level in third tertile | 24.4 (19.3–30.5) | 8.1 | 21.4 (17.4–23.1) | 504 000 |

Subjects with ADHD met DSM-IV criteria for any ADHD subtype.

^a Models were adjusted for current household smoke exposure, gender, age, race/ethnicity, income, preschool attendance, mother's age at child's birth, and birth weight.

sure was based on caregiver reports, rather than a biological marker.⁷¹ However, some previous studies suggested high reliability of maternal reports of smoking during pregnancy,⁷² with limited evidence for underreporting.^{73–76} Furthermore, because social desirability response bias favors misclassification of subjects who smoked during pregnancy as nonsmokers, which likely would attenuate smoking effects, it is notable that we still documented significant effects of prenatal tobacco exposure on ADHD. Additional limitations include our use of a dichotomous variable (yes/no) to measure prenatal tobacco exposure, which rendered us unable to assess dose-response and timing effects.^{40,77} These limitations underscore the need for future studies incorporating biomarkers of prenatal tobacco exposure and longitudinal assessment from the prenatal period to later childhood, such as in the National Children's Study.⁷⁸

Furthermore, we studied the relationship between ADHD and current, rather than peak, lead levels. However, this may prove to be a strength rather than a weakness, given the accumulating evidence that current blood lead levels are stronger predictors of cognitive outcomes than are peak levels.^{48,79,80} We were unable to determine the association between the toxicant exposures and specific ADHD subtypes because of limited sample size, and

we did not have genetic information available for assessment of gene-environment interactions. Future studies with considerable sample sizes are needed to examine whether the toxicant exposures are associated with specific ADHD subtypes and/or endophenotypes^{12,24,81} and whether certain genetic subgroups are particularly susceptible to ADHD in the setting of lead⁵³ and prenatal tobacco^{16,82,83} exposures. The study of joint toxicant-gene effects seems particularly promising, because Neuman et al¹⁶ recently documented that prenatally smoke-exposed children carrying both the high-risk dopamine transporter (*DAT*) and dopamine D₄ receptor (*DRD4*) alleles had an elevated odds ratio of 9.0 for population-defined ADHD, combined subtype. Finally, it was beyond the scope of this cross-sectional study to determine what effect decreases in prenatal tobacco and childhood lead exposures over time might have had on ADHD rates. Numerous factors complicate investigation of US changes in ADHD prevalence over time, including changing ADHD diagnostic criteria and heightened awareness of the disorder.

CONCLUSIONS

We found that prenatal tobacco and childhood lead exposures may be significant risk factors for ADHD, especially when individuals are exposed to both toxicants. Although the United States has made considerable strides

in reducing these toxicant exposures, 15% of women reported smoking during pregnancy in a large, US population-based study in 2004,⁸⁴ and an estimated 1.6% of US children had blood lead levels above the Centers for Disease Control and Prevention level of concern ($\geq 10 \mu\text{g/dL}$) in 1999–2002, with almost 14% having levels of 5 to 9 $\mu\text{g/dL}$.⁸⁵ Our findings suggest that reduction of toxicant exposures may be an important avenue for ADHD prevention, and they underscore the enormous burden that may be associated with continued exposure to tobacco and lead.

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**Association of Tobacco and Lead Exposures With
Attention-Deficit/Hyperactivity Disorder**

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