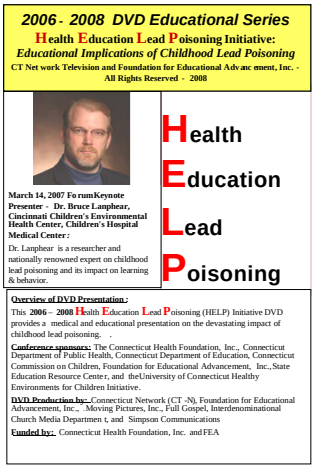
HEALTH EDUCATION LEAD POISONING (*H.E.L.P.*)

On-Line Professional Development CEU Course Series

Module # 4 - Supplementary Readings

Dr. Bruce Lanphear



Research Studies and Articles

Below are the following Health Education Lead Poisoning (H.E.L.P.) On-Line CEU Course Module Supplementary Readings:

1) Childhood Lead Exposure Associated with Criminal Behavior

2) Science News: Childhood Lead Exposure Linked to Criminal Behavior in Adulthood

3) Lead in Kids: Violent Crimes Appear Linked

4) Decreased Brain Volume in Adults with Childhood Lead Exposure

5) Association of Prenatal and Childhood Blood Lead Concentrations with Criminal Arrests in Early Adulthood - **Website Address:** http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0050101

6) "Low-Level Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis**" - Environmental Health Perspectives** – ***Volume 113 Number 7, July 2005***

7) "Exposures to Environmental Toxicants and Attention Deficit Hyperactivity Disorder in U.S. Children" - **Environmental Health Perspectives** - *Volume 114,* ***Number 12, December 2006***

8) "Intellectual Impairment in Children with Blood Lead Concentrations below 10 µg per Deciliter", The New England Journal of Medicine, *Vol. 348, Number 16 - April 17 , 2003*

9) Curriculum Vitae - Dr. Bruce Lanphear

Childhood Lead Poisoning Association with Criminal Behavior in Adulthood

Public release date: 27-May-2008 Contact: Amanda Harper, University of Cincinnati

University of Cincinnati Kim Dietrich - Lead Exposure linked to Delinquency and Juvenile Crime

CINCINNATI—New research from the University of Cincinnati (UC) reports the first evidence of a direct link between prenatal and early-childhood lead exposure an increased risk for criminal behavior later in life.

Kim Dietrich, Ph.D., is a professor of environmental health at the University of Cincinnati College of Medicine. He is principal investigator of the Cincinnati lead cohort study.

Based on long-term data from a childhood lead study in Cincinnati, Ohio, Kim Dietrich, PhD, and his team have determined that elevated prenatal and postnatal blood-lead concentrations are associated with higher rates of criminal arrest in adulthood.

“Previous studies either relied on indirect measures of exposure or failed to follow subjects into adulthood to examine the relationship between lead exposure and criminal activity in young adults,” explains Dietrich, principal investigator of the study and professor of environmental health at UC.

“We have monitored this specific sub-segment of children who were exposed to lead both in the womb and as young children for nearly 30 years,” he adds. “We have a complete record of the neurological, behavioral and developmental patterns to draw a clear association between early-life exposure to lead and adult criminal activity.”

Bruce P. Lanphear, M.D., M.P.H. is the Sloan Professor of Children's Environmental Health and Professor of Pediatrics at Cincinnati Children's Hospital Medical Center and the University of Cincinnati. Dr. Lanphear is director of the Cincinnati Children's Environmental Health Center located at Cincinnati Children's. He is a member of the U.S. EPA's Clean Air Scientific Advisory Committee Lead Review Panel and a Member of the National Children's Study Steering Committee.

Dietrich says few studies have attempted to evaluate the consequences of childhood lead exposure as a risk of criminal behavior. The UC-led study is the first of its kind to demonstrate an association between developmental exposure to lead and adult criminal behavior.

Dietrich and his colleagues report their findings in the May 27, 2008, issue of the journal Public Library of Science (PLOS) Medicine.

This new study is part of a long-term lead exposure study conducted through the Cincinnati Children’s Environmental Health Center, a collaborative research group funded by the National Institute of Environmental Health Sciences (NIEHS) and U.S. Environmental Protection Agency (EPA) that involved scientists from the UC College of Medicine and Cincinnati Children’s Hospital Medical Center.

Led by Dietrich, researchers recruited pregnant women living in Cincinnati neighborhoods with a higher concentration of older, lead-contaminated housing. Recruitment took place at four prenatal clinics between 1979 and 1984. Dietrich’s team has monitored this population group since birth to assess the long-term health effects of early-life lead exposure.

Of the original 376 newborns recruited, 250 were identified for the current study. Researchers measured blood-lead levels during pregnancy and then at regular intervals until the children were 6 ½ years old to calculate cumulative lead exposure.

Blood-lead level data was then correlated with public criminal arrest records from a search of Hamilton County, Ohio, criminal justice records. These records provided information about the nature and extent of arrests and were coded by category: violent, property, drugs, fraud, obstruction of justice, serious motor vehicle, disorderly conduct and other offenses.

Researchers found that individuals with increased blood-lead levels before birth and during early childhood had higher rates of arrest—for both violent and total crimes—than the rest of the study population after age 18.

Approximately 55 percent of the subjects had at least one arrest—the majority of which involved drugs (28 percent) or serious motor vehicle violations (27 percent). The strongest association between childhood blood-lead level and criminal behavior was for arrests involving acts of violence.

Dietrich says that although both environmental lead levels and crime rates in the United States have dropped in the past 30 years, they have not done so in a uniform way.

“Lower income, inner-city children remain particularly vulnerable to lead exposure,” he explains. “Although we’ve made great strides in reducing lead exposure, our findings send a clear message that further reduction of childhood lead exposure may be an important and achievable way to reduce violent crime.

“Aggressive or violent behavioral patterns often emerge early and continue throughout life,” adds Dietrich. “Identifying the risk factors that may place youth on an early trajectory toward a life of crime and violence should be a public health priority.”

Study coauthor John Wright, PhD, a member of UC’s criminal justice faculty who studies the impact of factors like genetics, psychology and biology on criminality, says he had limited expectations for how strong a correlation between lead exposure and criminality could be established.

“I did not expect we would see an effect, much less a substantive effect and even less likely a highly resilient effect,” says Wright. “The fact that we are able to detect the effects from childhood exposures now into adulthood stands as a testament of lead’s power to influence behavior over a long period of time.”

###

UC coauthors include M. Douglas Ris, PhD, Richard Hornung, PhD, Stephanie Wessel, Bruce Lanphear, MD, Mona Ho, and Mary Rae, PhD. Funding for the study came from grants from the NIEHS and U.S. EPA.

Science News

Childhood Lead Exposure Linked To Criminal Behavior in Adulthood

Science Daily (May 28, 2008) — New research from the University of Cincinnati (UC) reports the first evidence of a direct link between prenatal and early-childhood lead exposure an increased risk for criminal behavior later in life.

Based on long-term data from a childhood lead study in Cincinnati, Ohio, Kim Dietrich, PhD, and his team have determined that elevated prenatal and postnatal blood-lead concentrations are associated with higher rates of criminal arrest in adulthood.

"Previous studies either relied on indirect measures of exposure or failed to follow subjects into adulthood to examine the relationship between lead exposure and criminal activity in young adults," explains Dietrich, principal investigator of the study and professor of environmental health at UC.

"We have monitored this specific sub-segment of children who were exposed to lead both in the womb and as young children for nearly 30 years," he adds. "We have a complete record of the neurological, behavioral and developmental patterns to draw a clear association between early-life exposure to lead and adult criminal activity."

Children at play in a 1950s era tenement in Cincinnati, Ohio. (Credit: Cincinnati Historical Society)

Dietrich says few studies have attempted to evaluate the consequences of childhood lead exposure as a risk of criminal behavior. The UC-led study is the first of its kind to demonstrate an association between developmental exposure to lead and adult criminal behavior.

This new study is part of a long-term lead exposure study conducted through the Cincinnati Children's Environmental Health Center, a collaborative research group funded by the National Institute of Environmental Health Sciences (NIEHS) and U.S. Environmental Protection Agency (EPA) that involved scientists from the UC College of Medicine and Cincinnati Children's Hospital Medical Center.

Led by Dietrich, researchers recruited pregnant women living in Cincinnati neighborhoods with a higher concentration of older, lead-contaminated housing. Recruitment took place at four prenatal clinics between 1979 and 1984. Dietrich's team has monitored this population group since birth to assess the long-term health effects of early-life lead exposure.

Of the original 376 newborns recruited, 250 were identified for the current study. Researchers measured blood-lead levels during pregnancy and then at regular intervals until the children were 6 ½ years old to calculate cumulative lead exposure.

Blood-lead level data was then correlated with public criminal arrest records from a search of Hamilton County, Ohio, criminal justice records. These records provided information about the nature and extent of arrests and were coded by category: violent, property, drugs, fraud, obstruction of justice, serious motor vehicle, disorderly conduct and other offenses.

Researchers found that individuals with increased blood-lead levels before birth and during early childhood had higher rates of arrest--for both violent and total crimes--than the rest of the study population after age 18.

Approximately 55 percent of the subjects had at least one arrest--the majority of which involved drugs (28 percent) or serious motor vehicle violations (27 percent). The strongest association between childhood blood-lead level and criminal behavior was for arrests involving acts of violence.

Dietrich says that although both environmental lead levels and crime rates in the United States have dropped in the past 30 years, they have not done so in a uniform way.

"Lower income, inner-city children remain particularly vulnerable to lead exposure," he explains. "Although we've made great strides in reducing lead exposure, our findings send a clear message that further reduction of childhood lead exposure may be an important and achievable way to reduce violent crime.

"Aggressive or violent behavioral patterns often emerge early and continue throughout life," adds Dietrich. "Identifying the risk factors that may place youth on an early trajectory toward a life of crime and violence should be a public health priority."

Study coauthor John Wright, PhD, a member of UC's criminal justice faculty who studies the impact of factors like genetics, psychology and biology on criminality, says he had limited expectations for how strong a correlation between lead exposure and criminality could be established.

"I did not expect we would see an effect, much less a substantive effect and even less likely a highly resilient effect," says Wright. "The fact that we are able to detect the effects from childhood exposures now into adulthood stands as a testament of lead's power to influence behavior over a long period of time."

UC coauthors include M. Douglas Ris, PhD, Richard Hornung, PhD, Stephanie Wessel, **Bruce Lanphear, MD**, Mona Ho, and Mary Rae, PhD. Funding for the study came from grants from the NIEHS and U.S. EPA.

Journal reference:

1. Wright JP, Dietrich KN, Ris MD, Hornung RW, Wessel SD, et al. **Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood**. *PLoS Med*, 2008; 5(5): e101 DOI: 10.1371/journal.pmed.0050101

Adapted from materials provided by University of Cincinnati.

The Columbus Dispatch.com

Lead in kids, violent crime appear linked

Wednesday, May 28, 2008 4:20 AM

BY MISTI CRANE

THE COLUMBUS DISPATCH

FILE PHOTO | DISPATCH

Lead remains a health threat, particularly in poor communities where children are more likely to live in older homes that are in disrepair.

LEAD'S LEGACY

Exposure to lead in early childhood can shrink the brain and probably contributes to violent criminal activity in young adulthood, according to two studies arising out of a long-term effort to track lead's impact on children.

The studies are part of the Cincinnati Lead Study, which began in 1979 and has followed babies born in four clinics in poor areas of the city. The research was published in yesterday's edition of *PloS Medicine*, a journal published by the Public Library of Science.

Lead, once routinely found in gasoline, paint and other common materials, remains a health threat, particularly in poor communities where children are more likely to live in older homes that are in disrepair.

This research offers new and unique insight into the damage lead does, researchers said yesterday.

The higher the lead level in the body, the greater the chance a person would commit a crime, a team of researchers found.

That supports decades of research linking aggressive behavior with lead exposure, but it goes further because researchers were able to track people from before birth and build a stronger case that the lead caused the behavior, said Kim Dietrich, an epidemiologist and University of Cincinnati medical professor who led the research team.

The crime study included 250 participants and compared their lead levels in childhood with arrests in Hamilton County in their early adulthood.

The chances of committing a violent crime increased by 30 percent with each increase of 5 micrograms per deciliter in the average childhood level of lead in the blood, Dietrich said. Micrograms per deciliter is how doctors measure lead in the blood.

Researchers took into account potential confounding factors, including socioeconomic status, said Dietrich, who has been following the study participants since they were children.

"A lot have come back to me and complained about issues that I think are related to this problem -- issues with domestic relationships, trouble holding down a job or concentrating at work," he said.

The accompanying study, which examined the brains of 157 of the lead-study participants, found that the more exposure people had as children, the more brain mass they had lost by the time they were examined as young adults, said researcher Kim Cecil of Cincinnati Children's Hospital Medical Center.

The area of concern was the brain's frontal lobe, which helps people judge how their actions -- including crimes -- might affect someone else. Damage there prompts people to act more impulsively and struggle when trying to accomplish tasks that require considering multiple aspects of a situation, such as driving, Cecil said.

The discoveries open up many more questions, including whether the brain is damaged in youth and the damage remains stagnant, or the brain continues to degenerate after lead exposure, she said.

Brain loss of about 1 percent was much more common in men than women, Cecil said.

"Hopefully we're beginning to build some substantial body of evidence that some of these problems in society are related to preventable environmental exposure," said Patrick MacRoy, executive director of the Alliance for Healthy Homes, an advocacy group based in Washington, D.C. MacRoy said lead exposure should have been eliminated in the United States long ago.

RESEARCH ARTICLE

Open Access: http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371%2Fjournal.pmed.0050112

Decreased Brain Volume in Adults with Childhood Lead Exposure

Kim M. Cecil[1,2,3*], Christopher J. Brubaker[2], Caleb M. Adler[4], Kim N. Dietrich[1,5], Mekibib Altaye[3], John C. Egelhoff[2], Stephanie Wessel[1,5], Ilayaraja Elangovan[2], Richard Hornung[1,5], Kelly Jarvis[4], Bruce P. Lanphear[1,3,5]

1 Cincinnati Children's Environmental Health Center, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America, **2** Department of Radiology, University of Cincinnati College of Medicine, Cincinnati, Ohio, United States of America, **3** Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio, United States of America, **4** Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, Ohio, United States of America, **5** Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, Ohio, United States of America

Background

Although environmental lead exposure is associated with significant deficits in cognition, executive functions, social behaviors, and motor abilities, the neuroanatomical basis for these impairments remains poorly understood. In this study, we examined the relationship between childhood lead exposure and adult brain volume using magnetic resonance imaging (MRI). We also explored how volume changes correlate with historic neuropsychological assessments.

Methods and Findings

Volumetric analyses of whole brain MRI data revealed significant decreases in brain volume associated with childhood blood lead concentrations. Using conservative, minimum contiguous cluster size and statistical criteria (700 voxels, unadjusted $p < 0.001$), approximately 1.2% of the total gray matter was significantly and inversely associated with mean childhood blood lead concentration. The most affected regions included frontal gray matter, specifically the anterior cingulate cortex (ACC). Areas of lead-associated gray matter volume loss were much larger and more significant in men than women. We found that fine motor factor scores positively correlated with gray matter volume in the cerebellar hemispheres; adding blood lead concentrations as a variable to the model attenuated this correlation.

Conclusions

Childhood lead exposure is associated with region-specific reductions in adult gray matter volume. Affected regions include the portions of the prefrontal cortex and ACC responsible for executive functions, mood regulation, and decision-making. These neuroanatomical findings were more pronounced for males, suggesting that lead-related atrophic changes have a disparate impact across sexes. This analysis suggests that adverse cognitive and behavioral outcomes may be related to lead's effect on brain development producing persistent alterations in structure. Using a simple model, we found that blood lead concentration mediates brain volume and fine motor function.

Funding: This work was supported by grants from the National Institutes of Health, NIEHS P01 ES011261, NIEHS R01 ES015559 NIEHS R21 ES013524, NCI R01 CA112182, and the Environmental Protection Agency

R82938901. These respective agencies had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

Competing Interests: Two of the study's authors, BPL and RH, are on the editorial board of *PLoS Medicine*. BPL and KND sporadically serve as expert witnesses without personal financial gain.

Academic Editor: John Balmes, University of California San Francisco, United States of America

Citation: Cecil KM, Brubaker CJ, Adler CM, Dietrich KN, Altaye M, et al. (2008) Decreased Brain Volume in Adults with Childhood Lead Exposure. PLoS Med 5(5): e112 doi:10.1371/journal.pmed.0050112

Received: August 20, 2007; **Accepted:** April 9, 2008; **Published:** May 27, 2008

Abbreviations: ACC, anterior cingulate cortex; ADHD, attention deficit hyperactivity disorder; CLS, Cincinnati Lead Study; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; ROI, region of interest; SES, Hollingshead socioeconomic scale; VBM, voxel-based morphometry; VLPFC, ventrolateral prefrontal cortex

* To whom correspondence should be addressed. E-mail: kim.cecil@cchmc.org

EDITORS' SUMMARY

Background.

Lead is a highly toxic metal that is present throughout the environment because of various human activities. In particular, for many years, large amounts of lead were used in paint, in solder for water pipes, in gasoline, and in ceramic glazes. But, as the harmful health effects of lead have become clear, its use in these and other products has been gradually phased out. Breathing air, drinking water, or eating food that contains lead can damage almost every organ in the human body. The organ that is most sensitive to lead exposure is the brain, and children's brains are particularly vulnerable because they are still developing. Children who swallow large amounts of lead can develop widespread brain damage that causes convulsions and sometimes death. Children who are repeatedly exposed to low to moderate amounts of lead (e.g., through accidentally swallowing residues of old lead paint or contaminated soil) can develop learning or behavioral problems.

Why Was This Study Done?

Lead exposure has been linked with various types of brain damage. These include problems with thinking (cognition); difficulties with organizing actions, decisions, and behaviors (executive functions); abnormal social behavior (including aggression); and difficulties in coordinating fine movements, such as picking up small objects (fine motor control). However, we know little about how lead damages the brain in this way and little about which brain regions are affected by exposure to low to moderate levels of lead during childhood. In this study, the researchers wanted to test the possibility that childhood lead exposure might lead to shrinking ("volume loss") parts of the brain, particularly the parts that are crucial to cognition and behavior. They therefore studied the relationship between childhood lead exposure and adult brain volume. They also explored whether there is a relationship between brain volume and measures of brain functioning, such as fine motor control, memory, and learning assessed during adolescence.

What Did the Researchers Do and Find?

Between 1979 and 1984, the researchers recruited babies born in poor areas of Cincinnati, where there were many old, lead-contaminated houses, into the Cincinnati Lead Study. They measured their blood lead levels regularly from birth until they were 78 months old and calculated each child's average blood lead level over this period. They then used brain scans (known as magnetic resonance imaging, or MRI) to measure the brain volumes of the participants when they were 19–24 years old. The researchers found that exposure to lead as a child was linked with brain volume loss in adulthood, particularly in men. There was a "dose-response" effect—in other words, the greatest brain volume loss was seen in participants with the greatest lead exposure in childhood. The brain volume loss was most noticeable in a part of the brain called the prefrontal cortex—especially a region called the "anterior cingulate cortex." When they examined the relationship between brain volume and measures of brain functioning, they found a link between brain volume and fine motor control, but not with the other measures.

What Do These Findings Mean?

These findings indicate that childhood lead exposure is associated with brain volume loss in adults, in specific regions of the brain. These brain regions are responsible for executive functions, regulating behavior, and fine motor control. Lead exposure has a larger effect on brain volumes in men than in women, which might help to explain the higher incidence of antisocial behaviors among men than women. Overall, these findings may explain why children and adults who have a history of lead exposure have behavioral and other problems, and support ongoing efforts to reduce childhood lead exposure in the US and other countries.

Additional Information.

Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.0050112.

- A *PLoS Medicine* Perspective article by David Bellinger further discusses this study and a related paper on child exposure to lead and criminal arrests in adulthood
- Toxtown, an interactive site from the US National Library of Medicine, provides information on environmental health concerns including exposure to lead (in English and Spanish)
- The US Environmental Protection Agency provides information on lead in paint, dust, and soil and on protecting children from lead poisoning (in English and Spanish)
- Medline Plus and the US National Library of Medicine Specialized Information Services provide lists of links to information on lead and human health (in English and Spanish)
- The US Centers for Disease Control and Prevention provides information about its Childhood Lead Poisoning Prevention Program
- The UK Health Protection Agency also provides information about lead and its health hazards

Introduction

Lead is widely recognized as a potent neurotoxicant, yet debate continues as to what levels of exposure result in irreversible brain injury. Evidence of lead "poisoning" is typically observed only at blood lead concentrations greater than 40 μg/dl (1.93 μmol/l) [1]. Encephalopathy is typically associated with blood lead concentrations greater than 100 μg/dl (4.83 μmol/l), but may occur at blood lead concentrations as low as 70 μg/dl (3.38 μmol/l), manifesting with focal lesions in the basal ganglia, thalami, cerebellum, cortical gray matter, and subcortical white matter [2–5]. Clinical neuroimaging studies in children with low to moderate (5 to 40 μg/dl [0.24 to 1.93 μmol/l]) blood lead concentrations tend to have few specific findings characteristic of lead exposure. However, such blood lead levels increase the individual likelihood of impaired cognition and executive function, impulsiveness, aggression, and delinquent behavior [6–11].

Converging lines of evidence suggest that these cognitive, motor, and behavioral changes result from exposure of the developing central nervous system (CNS) to lead [12–16]. Although the underlying mechanisms of neurotoxicity are complex, lead appears to alter neurotransmitter release, leading to excitotoxicity and ultimately apoptotic changes (reviewed in [15,17,18]).

Studies of adult organolead manufacturing workers have demonstrated that the past cumulative lead dose (estimated from lead concentration in tibia) was associated with cognitive test scores and measures of composite and regional brain volumes. For example, Stewart and colleagues report longitudinal declines in function and

stronger associations for decline in study participants with the apolipoprotein E 4 allele [19,20]. Analyses of brain images obtained with magnetic resonance imaging (MRI) indicate that smaller cingulate gyrus, insula, frontal gray matter, total gray matter, parietal white matter, and total brain volumes are associated with past cumulative lead doses decades after last occupational exposure [21]. These findings converge with a recent study showing that larger regional and composite brain volumes were associated with better cognitive function [22].

Despite the well-established link between lead exposure and cognitive deficits, few studies have directly examined the association between early childhood lead exposure and subsequent neurostructural features in adulthood. The purpose of this study was to investigate the effects of documented low to moderate childhood lead exposure, specifically mean childhood blood lead concentrations less than 40 μg/dl (1.93 μmol/l), on adult brain volume. We hypothesized that adults with higher childhood blood lead concentrations would demonstrate evidence of volume changes in neuroanatomical regions regulating cognitive and behavioral domains previously shown to be impaired with lead exposure. We also explored how volume changes correlate with factors derived from a comprehensive neuropsychological battery acquired during adolescence.

Methods / Participants

The individuals recruited for this investigation were participants in the Cincinnati Lead Study (CLS), an urban, inner-city cohort with detailed prenatal and postnatal histories of low to moderate lead exposure and behavioral outcomes monitored over 25 y. The CLS, a birth cohort recruited between 1979 and 1984, enrolled pregnant women who lived in neighborhoods with historically high rates of childhood lead poisoning. Exclusion criteria (see Text S1) for the mothers and infants were defined at study entry. This process netted newborns who were followed up quarterly through 5 y of age, semiannually from 5 to 6.5 y of age, again at age 10 y and between the ages of 15 and 17 y. A total of 157 CLS participants between the ages of 19 and 24 y provided informed consent and participated in this imaging study. A summary of their demographic features is presented in Table 1.

Table 1.

Characteristics of the Children and of their Mothers in the Cincinnati Lead Study (*n* = 157) with Comparison by Sex

Imaging Analysis Approach

We acquired whole-brain, three-dimensional, high-resolution 1.5 Tesla MRI data (see Text S1 for the detailed imaging protocol) to assess global and regional changes in brain tissue (gray matter, white matter, and cerebrospinal fluid [CSF]) volume for comparison with the mean of childhood blood lead concentrations

(measured in μg/dl) collected between 3 and 78 mo of life using voxel-based morphometry (VBM) [23]. VBM involves normalizing individual structural MRI scans to a study-specific template to allow voxel-by-voxel comparisons between individuals. This approach allows for advanced statistical analysis throughout the brain and does not rely on the a priori designation of structures of interest or manual tracing or segmentation of brain structures. Consequently, VBM is well suited to our investigational study of the effects of lead exposure on brain volume.

Blood lead concentrations (μg/dl) were measured in this cohort every 3 mo from birth for the first 5 y of life and every 6 mo from 5 to 6.5 y. To represent lead dose, the mean of the 23 childhood blood lead assessments for each participant was employed for our analyses. While peak and annual composite measures of quarterly assessments were available, we regarded the arithmetic mean childhood blood lead concentration as best representing individual cumulative lead exposure for the participants. The mean childhood blood lead concentrations have been previously reported and used consistently in the publications regarding the CLS cohort [9,24]. When no blood lead data were obtained from a given time point, the missing values were imputed from a weighted average of a within-individual regression of blood lead on age and the cohort mean at each age. This imputation was performed to avoid simply excluding those participants who may have one or only a few missing blood lead values in the context of an otherwise data-rich exposure history. Analyses demonstrated that there were no significant differences in magnitude, direction, or statistical significance of blood lead regression coefficients when observed and imputed datasets were compared with observed-only datasets.

For our VBM analysis, we developed multiple regression models of volume for each tissue class (gray matter, white matter, and CSF) and mean childhood blood lead as the covariate of interest. A simple regression analysis identifies regions of interest (ROIs) where volume change is associated with lead dose. We analyzed the data for evidence of volume changes in both directions: gain and loss. Because of the numerous factors involved in brain development that could alter composite and regional brain volumes, we evaluated multiple variables for inclusion in the regression models. These variables have also been implicated as alternative and/or additive factors responsible for the cognitive and behavioral manifestations attributed to lead dose. Variables considered include participant age at time of imaging, current marijuana use (obtained from a urine drug screening collected at time of imaging), sex, birth weight, gestational age at birth, maternal IQ [25], maternal alcohol consumption during pregnancy, maternal marijuana use during pregnancy, maternal tobacco use during pregnancy, mean childhood Hollingshead socioeconomic status (SES) score [26], current SES score, and home environment (using the mean Home Observation for Measurement of the Environment score measured in early childhood [27]). Upon adding an individual putative confounder variable into the otherwise simple linear regression between volume and mean childhood blood lead concentration, the change of regression coefficient (beta) was calculated to evaluate the influence of the variable. This testing was conducted within the ROIs significantly correlated (unadjusted $p \leq 0.001$; 700 voxel cluster threshold) with the mean childhood blood lead concentration. The variable was considered significant and retained for the subsequent final multivariate analysis if adding the variable caused greater than 20% of the pixels for the composite ROIs to have over a 10% change in the beta values. Two variables—age at

time of imaging and birth weight—satisfied the criteria for inclusion and were included in the final multiple regression model. The effect of sex on lead-associated volumetric changes was assessed by testing for a sex-by-lead interaction in the whole cohort as well as in separate analyses for males and females. (Additional details are included in Text S1.)

Exploratory Analysis of Neuropsychological Outcome

The data collected from the CLS participants at the time of enrollment in the imaging study did not include neuropsychological measures. However, the factors for adolescent (approximately 15.6 y old) neuropsychological measures as described by Ris, and colleagues [28] were available for exploring the relationship of our structural data with functional outcomes. The overlap of the adolescent and adult waves of the CLS resulted in 120 participants having both brain imaging data (n = 157) and neuropsychological factor scores (n = 195). For these additional volumetric analyses, we took as the outcome measure the individual factor scores for the five categories: memory, learning/IQ, attention, visuoconstruction, and fine motor, and compared it with gray matter images covarying for sex. As with the primary analyses, regional increases and decreases in gray matter volume associated with respective factor scores were determined. Subsequently, the addition of 78-mo blood lead concentration as a covariate into the models would add negative volume associations to the respective model, effectively nulling common territories. As this represents an exploratory analysis, no variables other than sex were examined as possible covariates.

Ethical Oversight

The institutional review boards of the Cincinnati Children's Hospital Medical Center and the University of Cincinnati approved the study protocol. A Certificate of Confidentiality for the study was obtained from the National Institutes of Health.

Results

Higher mean childhood blood lead concentrations were associated with significant decrements in gray matter volume for several cortical regions (Figure 1; Table 2). The volumetric-based analysis revealed an inverse, linear dose-effect relationship between mean childhood blood lead concentration and brain volume in specific regions. (Figure 2). Prefrontal cortical areas of lead-related volumetric decline involved the medial and the superior frontal gyri comprising the ventrolateral prefrontal cortex (VLPFC) as well as the anterior cingulate cortex (ACC). Other areas of lead-related volume loss were located in postcentral gyri, the inferior parietal lobule, and the cerebellar hemispheres. Using conservative, minimum contiguous cluster size and statistical criteria (700 voxels, unadjusted $p < 0.001$), approximately 1.2% of the total gray matter was significantly and inversely associated with mean childhood blood lead concentration. No significant volume changes were observed within white matter or CSF volume.

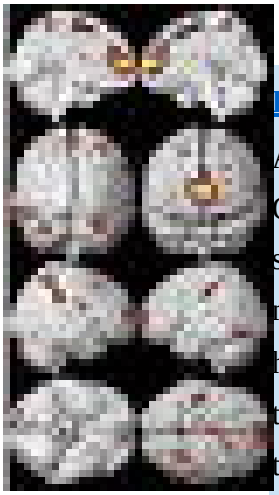


Figure 1. Regional Brain Volume Loss for the Cincinnati Lead Study Participants

A composite representation of regions with significant volume loss for male and female CLS participants (n = 157) associated with mean childhood blood lead concentrations is shown with red and yellow clusters overlaid upon a standard brain template (seen at multiple angles; the first row presents views from the midline of the left and right hemispheres, respectively; the second row demonstrates views from the back and front of the cerebrum, respectively; the third row shows the lateral right and left hemispheres; and the fourth row shows views from below and above the cerebrum. Brain template source reference [51].

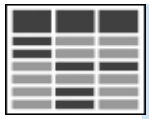


Table 2.

Coordinates of Significant Lead Associated Volume Loss for the CLS Participants

Figure 2. Regional Brain Volume Loss for the Cincinnati Lead Study Participants

The relationship of individual brain volume with mean childhood blood lead concentrations within a medial frontal cluster is illustrated by this plot. The model is adjusted for age at time of scanning and birth weight, using a cluster threshold of 700 voxels and unadjusted $p \leq 0.001$.

To explore the functional significance of these results, we compared neuropsychological factor scores and gray matter volume for the cohort. The analyses showed that the fine motor factor provided the strongest association, as it demonstrates a positive gray matter volume effect at a statistical threshold of $p < 0.001$ and minimum cluster of 700 voxels. The primary regions with this positive correlation included the cerebellar hemispheres bilaterally. These cerebellar regions correspond very well with the established, classical functional neuroanatomy implicated in the control of fine motor tasks (finger tapping and grooved peg board) comprising this factor. We found that the addition of the 78-mo blood lead concentration eliminated the association of fine motor function with cerebellar gray matter volume (Figure 3). Other factor scores (attention, visuoconstruction, memory, and learning/IQ) did not demonstrate such robust results with this simple overlap and elimination when adding lead into the sex-adjusted models

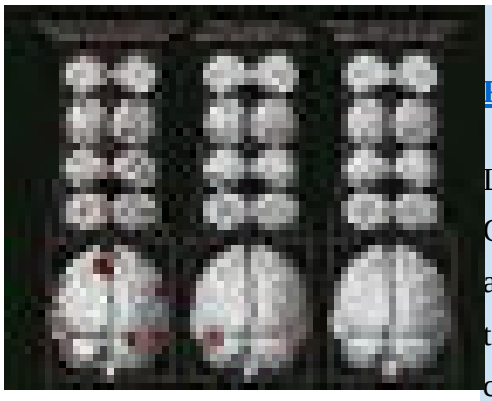


Figure 3. Structure-Function Relationship

Left, a composite representation of regions with significant volume loss for CLS participants associated with blood lead concentration at 78 mo of age and adjusted for sex is shown in red and yellow overlaid upon a standard brain template with the posterior coronal view highlighted below. Middle, analogous composite representation of regions with significant volume gain associated with fine motor factor scores and adjusted for sex. Right, analogous composite representation of regions with significant volume gain associated with fine motor factor scores, adjusted for sex and blood lead concentration at 78 mo of age. Brain template source reference [51]. In analyses stratified by sex, male participants demonstrated gray matter volume loss, primarily within the VLPFC and ACC (Figure 4). Again, using conservative minimum contiguous cluster size and statistical criteria (700 voxels, unadjusted $p < 0.001$), approximately 1.7% of the total gray matter volume loss of males was significantly and inversely associated with mean childhood blood lead concentration. In contrast, female participants demonstrated no significant gray matter volume loss in separate sex interaction models, with only a small parietal lobe foci represented (Figure 5). Notably, regions of gray matter volume loss in males were larger and more statistically significant than in the entire cohort, particularly within the frontal lobes. The mean childhood blood lead concentration did not significantly differ between the male (13.5 μg/dl [0.065 μmol/l], SD 6.3 μg/dl) and female participants (13.1 μg/dl [0.063 μmol/l], SD 5.5 μg/dl) ($t = 0.67$, $p = 0.50$). No demographic variables significantly differed between male and female participants.

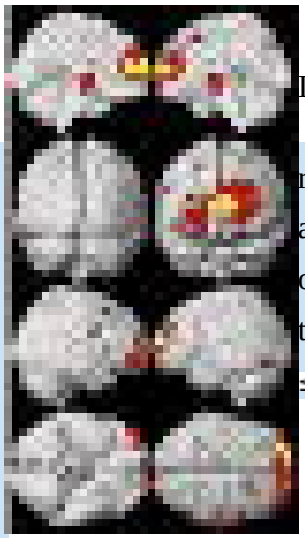
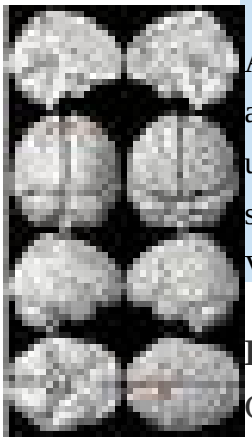


Figure 4. Sex Influences Brain Volume Loss Associated with Lead Exposure (Males)

A composite representation of regions with significant volume loss for CLS participants associated with mean childhood blood lead concentrations is shown in red and yellow overlaid upon a standard brain template for males ($n = 83$). The model is adjusted for age at time of scanning and birth weight, using a cluster threshold of 700 voxels and unadjusted $p \leq 0.001$. Views are the same as shown in Figure 1; brain template source reference [51].

Figure 5. Sex Influences Brain Volume Loss Associated with Lead Exposure (Females)



A composite representation of regions with significant volume loss for CLS participants associated with mean childhood blood lead concentrations is shown in red and yellow overlaid upon a standard brain template for females (n = 74). The model is adjusted for age at time of scanning and birth weight, using a cluster threshold of 700 voxels and unadjusted $p \leq 0.001$. Views are the same as shown in Figure 1; brain template source reference [51].

Discussion

Our study showed that higher mean childhood blood lead concentration is associated with region-specific reductions in adult gray matter volume. The findings suggest that childhood lead exposure is associated with volume loss in considerable portions of the prefrontal cortex, including the ACC and the VLPFC. The ACC, a component of the brain's limbic system positioned about the rostrum of the corpus callosum, processes cognitive and emotional information separately with distinguishable territories (reviewed in [29]). The functions attributed to the cognitive subdivision, located in the dorsal aspects of the ACC, include modulating attention and executive functions via sensory and/or response selection [29]. Additional attributed functions include anticipation of cognitively demanding tasks, error detection, monitoring completion, assessing potential conflicts, complex motor control, performing new behaviors, motivation and reward-based decision making [30–32]. The affective and emotional division, which is located ventrally, is associated with regulation of personal and social behavior, decision-making, and emotional responses. VLPFC has also been suggested as being similarly associated with mood regulation [33,34].

Volume loss in all of the aforementioned frontal brain regions, including both the cognitive and emotional territories of the ACC (Brodmann areas detailed in Table 2), is consistent with and potentially explanatory for cognitive and behavioral problems previously associated with lead exposure [8,12–14,28,35,36].These problems include general intellectual and executive functioning, antisocial behaviors, and attention deficit hyperactivity disorder (ADHD). Some studies report a structure–function relationship, which ultimately translates as brain volume change corresponding with altered function. In analyses of brain volumes and measures of cognitive function in adult organolead manufacturing workers, Schwartz and colleagues [22] showed that larger ROI volumes were associated with better cognitive function in five of six cognitive domains (visuoconstruction, processing speed, visual memory, executive functioning, and eye–hand coordination). Recent studies by Raine and colleagues suggest that deficits in cortical volume or activity found in select brain regions, such as prefrontal gray matter, may predispose a person to impulsive, aggressive, or violent behavior [37–39]. However, it is important to note that not all pathologies produce such straightforward correlations between structure and function, as some cognitive and behavioral functions are diffusely distributed such that the effects of other confounders (e.g., age) show greater influence on structural volumes [40].

Previously, Dietrich and colleagues reported the motor developmental status in 245 children of the CLS cohort at 6 y of age [9]. Following statistical adjustment for covariates, neonatal blood lead levels were associated with poorer

performance on a measure of upper-limb speed and dexterity and the fine-motor composite. Postnatal blood lead levels remained significantly associated with poorer scores on measures of bilateral coordination, visual-motor control, upper-limb speed and dexterity, and the fine-motor composite. The strongest and most consistent relationships were observed with concurrent blood lead levels (mean 10.1 μg/dl [SD 5.6]). A 10 μg/dl increase in concurrent blood lead levels was associated with a 4.6 point (95% CI 2.1–7.1) decline in the fine motor composite score. The 78-mo postnatal blood lead levels were significantly associated with poorer fine-motor skills as indexed by covariate-adjusted factor scores derived from a factor analysis of a comprehensive neuropsychological battery conducted at 16 y of age [34]. The variables loading highly on the fine-motor component came from the grooved pegboard and finger tapping tasks. Following covariate pretesting and adjustment, the principal finding reported from the study was a significant main effect of 78-mo blood lead on the fine motor factor [34]. We now observe that the fine motor factor also provided the strongest association between brain structure and function in our exploratory analysis. The fine motor factor shows a *positive* brain volume association at the same statistical threshold ($p < 0.001$ and minimum cluster of 700 voxels) as our primary result. Upon the addition of 78-mo blood lead concentrations, we found that the association between gray matter volume in the cerebellum and the fine motor factor was eliminated. The regional concordance of the fine motor factor and lead volume effect in the cerebellum may reflect the fact that motor developmental outcomes are more sensitive indicators of lead's adverse effects on the CNS and are probably less confounded with social factors than cognitive, academic, and behavioral outcomes [9].

The largest area of significant volume loss associated with childhood lead exposure includes medial portions of the prefrontal cortex. Synaptic overproduction in the medial frontal lobe reaches a maximum between 3 and 4 y of age with synaptic pruning occurring in mid-to-late adolescence [41]. During the first 5 y of life, at least one of the quarterly blood lead assessments exceeded 10 μg/dl (0.48 μmol/l) for 99% of the cohort. The peak lead exposure occurred between 2 and 3 y of age for the participants. By adolescence, the mean blood lead concentrations for the cohort were 2.8 μg/dl (1.35 μmol/l) (SD 1.3 μg/dl). Given this critical time period in brain development and maturation with documented low to moderate level of lead exposure in the CLS cohort, the finding of reduced volume within the medial frontal lobe of the adult brains associated with increased childhood blood lead concentration is consistent with lead exposure impairing cortical development and maturation. Our findings also suggest that this structural change is permanent. Additional studies will be necessary to narrow the time points and possibly thresholds of irreversible injury, as our analyses reflect cumulative childhood lead dose. This finding is also consistent with experimental data indicating that low-level lead exposure causes significant reduction in neurite length in dopaminergic neurons [42]. However, the changes in volume detected by the VBM method could represent a variety of changes (i.e., neuronal size, reductions of dendritic arborization, or changes in neuropil) at the cellular level [43]. Experimental models with pathological analyses and possibly imaging studies could further complement the changes revealed by the findings of this VBM study. In addition, several studies using animal models suggest that lead exposure alters the formation and maintenance of myelin [15,44–46]. In our analyses, no changes in white matter volume were observed. However, while axonal and myelin volume are maintained, myelin organization may be altered as a result of lead exposure. Future studies with diffusion tensor imaging are needed to

evaluate axonal and myelin integrity, since this method reveals quantitative information about the diffusion of water molecules about the myelin sheath of axons (see review [47]).

Evidence from behavioral studies in the CLS cohort, other epidemiological cohorts, and animal models indicate that males are more vulnerable to the effects of lead on executive function [28,36]. The higher incidence of ADHD and antisocial behaviors in males may be similarly consistent with greater susceptibility to childhood lead exposure. Froehlich and colleagues found that lead's effect on executive function arises from an interaction with the dopamine receptor D4 gene with exon III seven-repeat form (DRD4–7), with greater effect in males [36]. Braun and colleagues found that children with blood lead levels greater than 2 μg/dl (0.097 μmol/l), representing the top quintile of 4- to 15-y-old children in the United States, were four times more likely to have doctor-diagnosed ADHD [35]. Further studies are necessary to replicate our findings and provide clarification on the gene–environment interaction associated with greater vulnerability of males to lead exposure.

The significance and implications of the volume loss in the VLPFC and ACC in males are potentially profound. The increased sensitivity to lead in male participants has important sociological implications. Widely observed increases in rates of antisocial behaviors in young men no doubt are related to multiple cultural and biological factors, but negative behaviors in males may be exacerbated by the greater susceptibility of men to the toxic effects of lead exposure.

To our knowledge this is the first prospective study to directly examine the relationship between early exposure to lead and brain volume in adulthood. Lead dose as assessed by frequent serial blood lead determinations, assessment of a large number of potentially important covariate factors, and advanced imaging methods were unique aspects of this investigation. Furthermore, the sample was relatively homogenous with respect to sociodemographic variables such as SES and ethnicity, thus decreasing the extent to which strong confounding factors might generate spurious associations. In retrospect, a cumulative assessment of marijuana usage addressing the frequency and/or duration would have better characterized this potential confounder than urine screening for drug exposures at a single time point. Compared with VBM studies of psychiatric illnesses, we used a rigorous and conservative minimum contiguous cluster size and statistical criteria for significance (700 voxels, unadjusted $p < 0.001$) [33,48–50]. The VBM approach to quantifying brain volume eliminates bias from errors in the manual delineation of brain structures found with tracing studies. However, the VBM approach faces challenges in preprocessing of individual brains for group analyses; these limitations have been well described in the imaging literature (see Mechelli et al. [43]).

In summary, we found that early childhood lead exposure is associated with structural volume loss in the brain. The injury affects brain regions classically considered responsible for executive function, behavioral regulation, and fine motor control.We found that this volume loss persisted into adulthood. Our findings are consistent with and potentially explanatory for long-observed behavioral findings in children and adults with a history of lead exposure. Furthermore, decrements in brain volume associated with lead exposure were primarily present for male participants, independent of sex-related differences in blood lead concentrations and other demographic factors.

Supporting Information

Text S1. Detailed Descriptions of the Cincinnati Lead Study Population and Imaging Methods

(82 KB DOC)

Acknowledgments

The authors acknowledge the efforts of the MRI technologists Kendall J. O'Brien, BS, RT; and R. Scott Dunn, RT for providing imaging technical support. We are also grateful to members of the Cincinnati Lead Study Cohort and their families for their participation in this research.

Author contributions. KMC, CJB, KND, and BPL designed the experiments/the study. CJB, KND, JCE, and SW collected data or did experiments for the study. KMC, CJB, CMA, KND, MA, IE, and KJ analyzed the data. KMC, KND, and SW enrolled patients. KMC wrote the first draft of the paper. KMC, CJB, CMA, SW, RH, and BPL contributed to writing the paper. CJB designed part of the experiments/study and performed all the analysis. JCE reviewed the MRI studies. KMC, KND, and BPL participated in original conception of study, study design, and interpretation of results.

References

1. Staudinger KC, Roth VS (1998) Occupational Lead Poisoning. American Family Physician 57: 719–726. **FIND THIS ARTICLE ONLINE**
2. al Khayat A, Menon NS, Alidina MR (1997) Acute lead encephalopathy in early infancy–clinical presentation and outcome. Ann Trop Paediatr 17: 39–44. **FIND THIS ARTICLE ONLINE**
3. Mani J, Chaudhary N, Kanjalkar M, Shah PU (1998) Cerebellar ataxia due to lead encephalopathy in an adult. J Neurol Neurosurg Psychiatry 65: 797. **FIND THIS ARTICLE ONLINE**
4. Atre AL, Shinde PR, Shinde SN, Wadia RS, Nanivadekar AA, et al. (2006) Pre- and posttreatment MR imaging findings in lead encephalopathy. AJNR Am J Neuroradiol 27: 902–903. **FIND THIS ARTICLE ONLINE**
5. Tuzun M, Tuzun D, Salan A, Hekimoglu B (2002) Lead encephalopathy: CT and MR findings. J Comput Assist Tomogr 26: 479–481. **FIND THIS ARTICLE ONLINE**
6. Canfield RL, Henderson CR Jr., Cory-Slechta DA, Cox C, Jusko TA, et al. (2003) Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter. N Engl J Med 348: 1517–1526. **FIND THIS ARTICLE ONLINE**
7. Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, et al. (2005) Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ Health Perspect 113: 894–899. **FIND THIS ARTICLE ONLINE**
8. Canfield RL, Gendle MH, Cory-Slechta DA (2004) Impaired neuropsychological functioning in lead-exposed children. Dev Neuropsychol 26: 513–540. **FIND THIS ARTICLE ONLINE**

9. Dietrich KN, Berger OG, Succop PA, Hammond PB, Bornschein RL (1993) The developmental consequences of low to moderate prenatal and postnatal lead exposure: intellectual attainment in the Cincinnati Lead Study Cohort following school entry. Neurotoxicol Teratol 15: 37–44. **FIND THIS ARTICLE ONLINE**
10. Bellinger DC, Stiles KM, Needleman HL (1992) Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study. Pediatrics 90: 855–861. **FIND THIS ARTICLE ONLINE**
11. Needleman HL, Gatsonis CA (1990) Low-level lead exposure and the IQ of children. A meta-analysis of modern studies. Jama 263: 673–678. **FIND THIS ARTICLE ONLINE**
12. Needleman HL, Riess JA, Tobin MJ, Biesecker GE, Greenhouse JB (1996) Bone lead levels and delinquent behavior. Jama 275: 363–369. **FIND THIS ARTICLE ONLINE**
13. Stretesky PB, Lynch MJ (2001) The relationship between lead exposure and homicide. Arch Pediatr Adolesc Med 155: 579–582. **FIND THIS ARTICLE ONLINE**
14. Stretesky PB, Lynch MJ (2004) The relationship between lead and crime. J Health Soc Behav 45: 214–229. **FIND THIS ARTICLE ONLINE**
15. Lidsky TI, Schneider JS (2003) Lead neurotoxicity in children: basic mechanisms and clinical correlates. Brain 126: 5–19. **FIND THIS ARTICLE ONLINE**
16. Finkelstein Y, Markowitz ME, Rosen JF (1998) Low-level lead-induced neurotoxicity in children: an update on central nervous system effects. Brain Res Brain Res Rev 27: 168–176. **FIND THIS ARTICLE ONLINE**
17. Bressler JP, Goldstein GW (1991) Mechanisms of lead neurotoxicity. Biochem Pharmacol 41: 479–484. **FIND THIS ARTICLE ONLINE**
18. Toscano CD, Guilarte TR (2005) Lead neurotoxicity: from exposure to molecular effects. Brain Res Brain Res Rev 49: 529–554. **FIND THIS ARTICLE ONLINE**
19. Stewart WF, Schwartz BS, Simon D, Bolla KI, Todd AC, et al. (1999) Neurobehavioral function and tibial and chelatable lead levels in 543 former organolead workers. Neurology 52: 1610–1617. **FIND THIS ARTICLE ONLINE**
20. Stewart WF, Schwartz BS, Simon D, Kelsey K, Todd AC (2002) ApoE genotype, past adult lead exposure, and neurobehavioral function. Environ Health Perspect 110: 501–505. **FIND THIS ARTICLE ONLINE**
21. Stewart WF, Schwartz BS, Davatzikos C, Shen D, Liu D, et al. (2006) Past adult lead exposure is linked to neurodegeneration measured by brain MRI. Neurology 66: 1476–1484. **FIND THIS ARTICLE ONLINE**
22. Schwartz BS, Chen S, Caffo B, Stewart WF, Bolla KI, et al. (2007) Relations of brain volumes with cognitive function in males 45 years and older with past lead exposure. Neuroimage 37: 633–641. **FIND THIS ARTICLE ONLINE**
23. Ashburner J, Friston KJ (2000) Voxel-based morphometry–the methods. Neuroimage 11: 805–821. **FIND THIS ARTICLE ONLINE**

24. Dietrich KN, Succop PA, Berger OG, Hammond PB, Bornschein RL (1991) Lead exposure and the cognitive development of urban preschool children: the Cincinnati Lead Study cohort at age 4 years. Neurotoxicol Teratol 13: 203–211. **FIND THIS ARTICLE ONLINE**
25. Silverstein AB (1985) Two- and four-subtest short forms of the WAIS-R: a closer look at validity and reliability. J Clin Psychol 41: 95–97. **FIND THIS ARTICLE ONLINE**
26. Cirino PT, Chin CE, Sevcik RA, Wolf M, Lovett M, et al. (2002) Measuring socioeconomic status: reliability and preliminary validity for different approaches. Assessment 9: 145–155. **FIND THIS ARTICLE ONLINE**
27. Bradley RH, Caldwell BM (1979) Home observation for measurement of the environment: a revision of the preschool scale. Am J Ment Defic 84: 235–244. **FIND THIS ARTICLE ONLINE**
28. Ris MD, Dietrich KN, Succop PA, Berger OG, Bornschein RL (2004) Early exposure to lead and neuropsychological outcome in adolescence. J Int Neuropsychol Soc 10: 261–270. **FIND THIS ARTICLE ONLINE**
29. Bush G, Luu P, Posner MI (2000) Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 4: 215–222. **FIND THIS ARTICLE ONLINE**
30. Braver TS, Barch DM, Gray JR, Molfese DL, Snyder A (2001) Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. Cereb Cortex 11: 825–836. **FIND THIS ARTICLE ONLINE**
31. Williams ZM, Bush G, Rauch SL, Cosgrove GR, Eskandar EN (2004) Human anterior cingulate neurons and the integration of monetary reward with motor responses. Nat Neurosci 7: 1370–1375. **FIND THIS ARTICLE ONLINE**
32. Davis KD, Taylor KS, Hutchison WD, Dostrovsky JO, McAndrews MP, et al. (2005) Human anterior cingulate cortex neurons encode cognitive and emotional demands. J Neurosci 25: 8402–8406. **FIND THIS ARTICLE ONLINE**
33. Adler CM, DelBello MP, Jarvis K, Levine A, Adams J, et al. (2007) Voxel-based study of structural changes in first-episode patients with bipolar disorder. Biol Psychiatry 61: 776–781. **FIND THIS ARTICLE ONLINE**
34. Strakowski SM, Delbello MP, Adler CM (2005) The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. Mol Psychiatry 10: 105–116. **FIND THIS ARTICLE ONLINE**
35. Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP (2006) Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. Environ Health Perspect 114: 1904–1909. **FIND THIS ARTICLE ONLINE**
36. Froehlich TE, Lanphear BP, Dietrich KN, Cory-Slechta DA, Wang N, et al. (2007) Interactive Effects of a DRD4 Polymorphism, Lead, and Sex on Executive Functions in Children. Biol Psychiatry 62: 243–249. **FIND THIS ARTICLE ONLINE**
37. Raine A, Lencz T, Bihrle S, LaCasse L, Colletti P (2000) Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. Arch Gen Psychiatry 57: 119–127 discussion 128–119. **FIND THIS ARTICLE ONLINE**

38. Yang Y, Raine A, Lencz T, Bihrle S, Lacasse L, et al. (2005) Prefrontal white matter in pathological liars. Br J Psychiatry 187: 320–325. **FIND THIS ARTICLE ONLINE**
39. Yang Y, Raine A, Lencz T, Bihrle S, LaCasse L, et al. (2005) Volume reduction in prefrontal gray matter in unsuccessful criminal psychopaths. Biol Psychiatry 57: 1103–1108. **FIND THIS ARTICLE ONLINE**
40. Tisserand DJ, Visser PJ, van Boxtel MP, Jolles J (2000) The relation between global and limbic brain volumes on MRI and cognitive performance in healthy individuals across the age range. Neurobiol Aging 21: 569–576. **FIND THIS ARTICLE ONLINE**
41. Huttenlocher PR (1979) Synaptic density in human frontal cortex - developmental changes and effects of aging. Brain Res 163: 195–205. **FIND THIS ARTICLE ONLINE**
42. Schneider JS, Huang FN, Vemuri MC (2003) Effects of low-level lead exposure on cell survival and neurite length in primary mesencephalic cultures. Neurotoxicol Teratol 25: 555–559. **FIND THIS ARTICLE ONLINE**
43. Mechelli A, Price CJ, Friston KJ, Ashburner J (2005) Voxel-Based Morphometry of the Human Brain: Methods and Applications. Current Medical Imaging Reviews 1: 105–113. **FIND THIS ARTICLE ONLINE**
44. Deng W, McKinnon RD, Poretz RD (2001) Lead exposure delays the differentiation of oligodendroglial progenitors in vitro. Toxicol Appl Pharmacol 174: 235–244. **FIND THIS ARTICLE ONLINE**
45. Dabrowska-Bouta B, Sulkowski G, Bartosz G, Walski M, Rafalowska U (1999) Chronic lead intoxication affects the myelin membrane status in the central nervous system of adult rats. J Mol Neurosci 13: 127–139. **FIND THIS ARTICLE ONLINE**
46. Coria F, Monton F (1988) Recovery of the early cellular changes induced by lead in rat peripheral nerves after withdrawal of the toxin. J Neuropathol Exp Neurol 47: 282–290. **FIND THIS ARTICLE ONLINE**
47. Mori S, Zhang J (2006) Principles of diffusion tensor imaging and its applications to basic neuroscience research. Neuron 51: 527–539. **FIND THIS ARTICLE ONLINE**
48. Adler CM, Levine AD, DelBello MP, Strakowski SM (2005) Changes in gray matter volume in patients with bipolar disorder. Biol Psychiatry 58: 151–157. **FIND THIS ARTICLE ONLINE**
49. Wilke M, Kaufmann C, Grabner A, Putz B, Wetter TC, et al. (2001) Gray matter-changes and correlates of disease severity in schizophrenia: a statistical parametric mapping study. Neuroimage 13: 814–824. **FIND THIS ARTICLE ONLINE**
50. Wilke M, Kowatch RA, DelBello MP, Mills NP, Holland SK (2004) Voxel-based morphometry in adolescents with bipolar disorder: first results. Psychiatry Res 131: 57–69. **FIND THIS ARTICLE ONLINE**
51. Toga AW, Thompson PM (2005) Brain atlases of normal and diseased populations. Int Rev Neurobiol 66: 1–54. **FIND THIS ARTICLE ONLINE**

RESEARCH ARTICLE OPEN ACCESS

Association of Prenatal and Childhood Blood Lead Concentrations with Criminal Arrests in Early Adulthood

Website Address: http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0050101

Authors: John Paul Wright[1], Kim N. Dietrich[2*], M. Douglas Ris[3], Richard W. Hornung[3], Stephanie D. Wessel[2], Bruce P. Lanphear[3], Mona Ho[3], Mary N. Rae[2]

1 Cincinnati Children's Environmental Health Center, Division of Criminal Justice, University of Cincinnati, Cincinnati, Ohio, United States of America, **2** Cincinnati Children's Environmental Health Center, Division of Epidemiology and Biostatistics, Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, Ohio, United States of America, **3** Cincinnati Children's Environmental Health Center, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio, United States of America

Background

Childhood lead exposure is a purported risk factor for antisocial behavior, but prior studies either relied on indirect measures of exposure or did not follow participants into adulthood to examine the relationship between lead exposure and criminal activity in young adults. The objective of this study was to determine if prenatal and childhood blood lead concentrations are associated with arrests for criminal offenses.

Methods and Findings

Pregnant women were recruited from four prenatal clinics in Cincinnati, Ohio if they resided in areas of the city with a high concentration of older, lead-contaminated housing. We studied 250 individuals, 19 to 24 y of age, out of 376 children who were recruited at birth between 1979 and 1984. Prenatal maternal blood lead concentrations were measured during the first or early second trimester of pregnancy. Childhood blood lead concentrations were measured on a quarterly and biannual basis through 6.5 y. Study participants were examined at an inner-city pediatric clinic and the Cincinnati Children's Hospital Medical Center in Cincinnati, Ohio. Total arrests and arrests for offenses involving violence were collected from official Hamilton County, Ohio criminal justice records. Main outcomes were the covariate-adjusted rate ratios (RR) for total arrests and arrests for violent crimes associated with each 5 μg/dl (0.24 μmol/l) increase in blood lead

concentration. Adjusted total arrest rates were greater for each 5 μg/dl (0.24 μmol/l) increase in blood lead concentration: RR = 1.40 (95% confidence interval [CI] 1.07–1.85) for prenatal blood lead, 1.07 (95% CI 0.88–1.29) for average childhood blood lead, and 1.27 (95% CI 1.03–1.57) for 6-year blood lead. Adjusted arrest rates for violent crimes were also greater for each 5 μg/dl increase in blood lead: RR = 1.34 (95% CI 0.88–2.03) for prenatal blood lead, 1.30 (95% CI 1.03–1.64) for average childhood blood lead, and 1.48 (95% CI 1.15–1.89) for 6-year blood lead.

Conclusions

Funding: This work was supported by grants from the National Institute of Environmental Health Sciences (PO1-ES011261 and RO1-ES015559–01) and the United States Environmental Protection Agency (R82938901). The funding agencies played no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: Two of the study's authors, BPL and RH, are on the editorial board of *PLoS Medicine*. BPL and KND sporadically serve as expert witnesses without personal financial gain.

Academic Editor: John Balmes, University of California San Francisco, United States of America

Citation: Wright JP, Dietrich KN, Ris MD, Hornung RW, Wessel SD, et al. (2008) Association of Prenatal and Childhood Blood Lead Concentrations with Criminal Arrests in Early Adulthood. PLoS Med 5(5): e101 doi:10.1371/journal.pmed.0050101

Received: August 14, 2007; **Accepted:** March 18, 2008; **Published:** May 27, 2008

Abbreviations: ADHD, attention deficit hyperactivity disorder; CI, confidence interval; RR, rate ratio; SES, socioeconomic status

* To whom correspondence should be addressed. E-mail: kim.dietrich@uc.edu

EDITORS' SUMMARY

Background.

Violent crime is an increasing problem in many countries, but why are some people more aggressive than others? Being male has been identified as a risk factor for violent criminal behavior in several studies, as have exposure to tobacco smoke before birth, having antisocial parents, and belonging to a poor family. Another potential risk factor for antisocial behavior as an adult is exposure to lead during childhood, although few studies have looked directly at whether childhood lead exposure is linked with criminal behavior in adulthood. Lead is a toxic metal that damages the nervous system when ingested or inhaled. It is present throughout the environment because of its widespread use in the past in paint, solder for water pipes, and gasoline. In 1978, 13.5 million US children had a blood lead level above 10 μg/dl, the current US Centers for Disease Control and Prevention blood lead level of concern (the average US blood lead level is 2 μg/dl). Lead paint and solder were banned in 1978 and 1986, respectively, by the US federal government; leaded gasoline was finally phased out in 1996. By 2002, only 310,000 US children had a blood lead level above 10 μg/dl. However, children exposed to lower levels of lead than this—through ingesting flakes or dust residues of old lead paint, for example—can have poor intellectual development and behavioral problems including aggression.

Why Was This Study Done?

Although some studies have suggested that childhood lead exposure is associated with later criminal behavior, these studies have often relied on indirect measurements of childhood lead exposure such as bone lead levels in young adults or a history of lead poisoning. Other studies that have measured childhood lead exposure directly have not followed their participants into adulthood. In this new study, the researchers investigate the association between actual measurements of prenatal and childhood blood lead concentrations and criminal arrests in early adulthood to get a clearer idea about whether early lead exposure is associated with subsequent violent behavior.

What Did the Researchers Do and Find?

Between 1979 and 1984, the researchers recruited pregnant women living in poor areas of Cincinnati, which had a high concentration of older, lead-contaminated housing, into the Cincinnati Lead Study. They measured the women's blood lead concentrations during pregnancy as an indication of their offspring's prenatal lead exposure and the children's blood lead levels regularly until they were six and half years old. They then obtained

information from the local criminal justice records on how many times each of the 250 offspring had been arrested between becoming 18 years old and the end of October 2005. The researchers found that increased blood lead levels before birth and during early childhood were associated with higher rates of arrest for any reason and for violent crimes. For example, for every 5 μg/dl increase in blood lead levels at six years of age, the risk of being arrested for a violent crime as a young adult increased by almost 50% (the "relative risk" was 1.48).

What Do These Findings Mean?

These findings provide strong evidence that early lead exposure is a risk factor for criminal behavior, including violent crime, in adulthood. One possibility, which the authors were unable to assess in this study, is that lead exposure impairs intelligence, which in turn makes it more likely that a criminal offender will be caught (i.e., arrested). The authors discuss a number of limitations in their study—for example, they probably did not capture all criminal behavior (since most criminal behavior does not lead to arrest). Although both environmental lead levels and crime rates have dropped over the last 30 years in the US, the overall reduction was not uniform—inner-city children remain particularly vulnerable to lead exposure. The findings therefore suggest that a further reduction in childhood lead exposure might be an important and achievable way to reduce violent crime.

Additional Information.

Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.0050101.

- A PLoS *Medicine* Perspective article by David Bellinger further discusses this study and a related paper on childhood lead exposure and brain volume reduction in adulthood
- Study researcher Kim Dietrich can be heard talking about "The Lethal Legacy of Lead", a brief MP3 about lead exposure and violent crime
- Toxtown, an interactive site from the US National Library of Medicine, provides information on environmental health concerns including exposure to lead (in English and Spanish)
- The US Environmental Protection Agency provides information on lead in paint, dust, and soil and on protecting children from lead poisoning (in English and Spanish)

- MedlinePlus provides a list of links to information on lead poisoning (in English and Spanish)
- The US Centers for Disease Control and Prevention provides information about its Childhood Lead Poisoning Prevention Program
- The UK Health Protection Agency also provides information about lead and its health hazards

Introduction

Early onset of aggressive or violent behavior is a precursor to a life course marred by limited social and educational achievement, incarceration, underemployment, and premature mortality [1,2]. These maladaptive behavioral patterns, which often emerge early in life, remain highly stable [3]. These facts highlight the importance of identifying risk factors that may place youth on an early developmental trajectory toward a career of crime and violence.

A meta-analysis of 34 independent studies identified and prioritized risk factors for serious, violent criminal behavior [4]. The most consistent risk factors were male gender, prenatal exposure to tobacco smoke, having antisocial parents, and low family socioeconomic status. In contrast, few studies have evaluated the consequences of childhood lead exposure as a risk factor for criminal behavior.

Some epidemiological studies have found a relationship between childhood lead exposure and antisocial behavior. In a study of Philadelphia youth, a history of lead poisoning was among the most significant predictors of adolescent delinquency and adult criminality in males [5]. Bone lead levels were associated with delinquent behavior in a retrospective cohort study of 11-year-old Pittsburgh children [6]. In Cincinnati, prenatal and childhood blood lead concentrations were associated with an increased risk for antisocial behavior and delinquency in adolescence [7]. Finally, elevated bone lead levels were observed in juvenile court–adjudicated delinquents residing in Allegheny County, Pennsylvania compared to matched controls [8]. These studies suggest that exposure to environmental lead during childhood is associated with the development of conduct problems and delinquent behavior. In consideration of these findings, it is noteworthy that a number of recent ecological investigations correlating leaded gasoline sales or atmospheric lead levels with crime rates also support an association between lead exposure and criminal behavior [9–12]. Questions remain, however, because these studies were cross-sectional (hence causality cannot be firmly established), relied on indirect measures of lead exposure, or did not follow participants into adulthood.

Here, we report the results of a long-term prospective study on the effects of one potential childhood risk factor of adult arrests, elevated prenatal and childhood blood lead concentrations.

Methods

Participants

The Cincinnati Lead Study (CLS) is a birth cohort recruited from late 1979 to early 1984. The CLS enrolled women in their first or early second trimester of pregnancy who attended four prenatal clinics within impoverished Cincinnati neighborhoods with a high concentration of older, lead-contaminated housing [13]. Women were excluded or ineligible if they were known to be addicted to drugs, were known to have diabetes or a neurological or psychiatric condition, or refused prenatal participation. Newborns were excluded if their gestational age was less than 35 wk, birth weight less than 1,500 g, Apgar score at 5 min less than 6, or if genetic or other serious medical issues were present at birth. This process netted 376 newborns who were recruited at birth (i.e., informed oral and written consent was obtained from the mother in the hospital and a blood lead sample was obtained from the newborn). Of these newborns 305 were developmentally examined at the CLS follow-up clinic when they were 3 and 6 mo of age [14]. They were followed up quarterly through age 5 y and semiannually from age 5 to 6.5 y [15].

A total of 250 CLS participants who were between 19 and 24 y of age and had been followed at least through the first 6 y of life participated in the current study. Thus, individuals in the current analysis had serial blood lead concentrations spanning the entire preschool and early school-age period of development. Written informed consent was obtained by the investigator or a senior member of the research staff at each stage of this longitudinal study after it was determined that the participant or the participant's legal guardian understood the nature of the research. This protocol has been reviewed and approved by the institutional review boards of the University of Cincinnati College of Medicine and the Cincinnati Children's Hospital Medical Center.

The 250 participants in this analysis were not substantially different from those with missing data with regard to baseline perinatal characteristics such as birth weight (3,134 versus 3,138 g), sex (50% versus 54% male), 6-y average Hollingshead [16] socioeconomic status (SES) total score (18.0 versus 18.3), years of maternal education (11.2 versus 11.1 y), scores on the Home Observation for Measurement of the Environment (the preschool version of a quantitative observational measure of early

nurturing and environmental stimulation [17]) (32.3 versus 33.4), and average childhood blood lead (13.4 versus 14.2 μg/dl).

Exposure and Outcome Assessments

We examined three measures of blood lead. Prenatal maternal blood lead concentration [μg/dl]) was measured during the first or early second trimester of pregnancy. Approximately 50% of the prenatal samples were obtained during the first trimester of pregnancy. The difference between maternal blood lead concentration assessed in the first and second trimesters was not statistically significant ($p = 0.76$) [14]. Postnatal blood lead indices included average childhood blood lead (average of 23 blood lead concentrations obtained quarterly from age 3 to 60 mo and semiannually from 66 to 78 mo), and 6.5-y blood lead. If a 6.5-y blood lead value was not available for a child, we used the blood lead test from 6 y. We selected 6.5 y blood lead over other serial blood lead measures because preliminary analyses indicated that blood lead measured at 6 y was more highly associated with the number of arrests than blood lead measured at other ages. Complete blood lead data were available for 89%–92% of the cohort at any particular quarterly assessment from 3 mo to 5 y of age. Missing postnatal blood lead concentrations were imputed from a weighted average of a within-participant regression of blood lead on age. This imputation was done to avoid excluding those participants who may have one or only a few missing blood lead tests. Prenatal blood lead concentrations were available for 87% (217/250) of the participants.

The primary outcome variable in this study was the individual's number of criminal arrests since turning 18 y of age. We did not collect data on convictions. Arrest is a more proximate measure of criminal behavior than are conviction data. Arrest typically occurs at the scene of the criminal event or immediately thereafter. Arrest decisions, moreover, usually reflect the seriousness of the offense, the offender's prior record, and the desire of the victim to have the individual arrested. Conversely, conviction data are distal indicators of criminal behavior. Actual criminal convictions derived from a trial represent less than 10% of all criminal arrests. Over 90% of all criminal cases are subject to plea bargaining, in which a plea of “guilty” is usually rewarded with a reduced charge and/or sentence. From the time of arrest it can take upward of 2 y or more before a defendant is tried in a court, or it can take over 1 y from the time of arrest to the time at which a plea deal is accepted by the court. Furthermore, a range of extra-legal variables can enter into the plea and trial process, including the defendant's economic status, support system, and access to quality defense counsel. We should also add that Hamilton County, Ohio (the study's catchment area) makes extensive use of “diversion” programs. These programs select individuals with specified problems or offenses, such as drunken driving or drug

abuse and “divert” them from jail or prison into community-based rehabilitation programs. Upon successful completion of the program and a probationary term, many of these programs “erase” the individual's legal conviction, but not the arrest. Finally, at least for this study, arrest data are substantially more complete than are conviction data. Arrest data in Hamilton County, Ohio are compiled into a single county-wide database and are updated at regular intervals. Court data, however, are not updated regularly. This problem is endemic to court systems nationwide, because courts operate at different levels (city, county, state, Federal) and are under the guidance of individual judges.

Data on Criminal Arrests

Data on criminal arrests for participants and their mothers were obtained from a computer search of Hamilton County, Ohio criminal justice records. These records provided information on the nature, number, and disposition of arrests. Two reviewers who were blind to participants' blood lead concentrations independently coded each arrest into one of the following categories: violent offenses (e.g., murder, rape, domestic violence, assault, robbery, or possession of a weapon); offenses against property (e.g., burglary or arson); drug offenses (e.g., trafficking, abuse, or possession); fraud; obstruction of justice; serious motor vehicle offenses (e.g., driving without a license, driving under the influence of alcohol, or driving under suspension); disorderly conduct; and other offenses, which included offenses that did not fit in any previously mentioned category. Minor motor vehicle offenses, such as speeding, safety restraint violations, lights burned out, failing to stop, and pedestrian offenses were excluded from the analyses. We counted the number of arrests and coded the nature of the offense that led to each arrest. If an individual was charged with more than one offense during a single arrest, then the most serious offense was used for classification. Thus, arrest counts were lower than the total number of offenses. Legally determined guilt was not a factor in our coding. Only those offenses that were filed before 31 October 2005 were included in the analyses.

Inter-reviewer differences with respect to arrest and category of offense were resolved by a third reviewer who conducted the initial training for criminal record coding. Interobserver agreement as assessed by Cohen's kappa was 0.93 for maternal offenses and 0.97 for participant offenses.

Statistical Analyses

We used negative binomial regression models to analyze these data because the counts of arrests were overdispersed when originally examined using Poisson regression models [18]. This model provided a very good fit to these data in terms of the estimated scale

parameter. These models were used to estimate the association between blood lead concentrations and arrest rates adjusted for other important risk factors. We calculated separate models for each blood lead measure. Our dependent variable was the number of criminal arrests for each participant measured as discrete counts, which were positively skewed. To account for the number of years at risk of arrest, we used the log of current age as an offset in all models. To control for potential confounding, we examined variables reflecting the effects of other neurotoxicants such as maternal cigarette and marijuana smoking and consumption of narcotics during pregnancy, as well as variables related to adult criminal involvement in prior studies. Our list of candidate covariates included: sex; a validated measure of the quality of early care-giving and environmental stimulation called the Home Observation for Measurement of the Environment (HOME) inventory score [17]; birth weight (g); maternal smoking during pregnancy (half-packs consumed per day); maternal alcohol, marijuana, or narcotic use (Y/N); maternal education level (highest grade); maternal IQ [19]; total prior maternal arrests; SES (average Hollingshead [16] score); number of children in the home; and whether the mother was on public assistance during the participant's childhood (Y/N). Data on fathers or male caregivers in the home were not available, since 84% of the households were headed by the mother or a male caregiver was not consistently present. Continuous covariates were examined using linear, polynomial, and log-transformed functions to assess whether simple linear terms were adequate for adjustment of covariate or confounder influences.

Candidate covariates or confounders remained in the final multivariable models if they were either statistically significant ($p \leq 0.05$) or if their inclusion in the model caused a change of $\geq$10% in the rate ratio estimates for lead, regardless of their level of statistical significance. We tested the interaction of lead by sex, since some studies have indicated that developing male central nervous systems may be more vulnerable than females' to environmental insults leading to later behavioral problems [20]. Before deciding upon a final multivariable model, regression diagnostics for collinearity and influence using the methods described in Belsley, et al. were employed [21]. As a measure of the absolute change in arrest rates between participants with higher levels of blood lead compared to those with lower blood lead levels, we defined attributable risk as the average difference in annual arrest rates between participants at the 95th percentile of blood lead and those at the 5th percentile. All significance tests were two-tailed. Results for blood lead variables are presented as adjusted rate ratios (RR) for total arrests and arrests for violent crimes. All statistical analyses were conducted with SAS (Statistical Analysis System), version 9.1 [22].

Results

The sample was largely African-American (90%), 50% of the participants were male, and 73% of families scored in the lowest two levels of the Hollingshead Four-Factor Index of Social Position [16]. A single female caregiver headed 84% of households.

Mean blood lead concentrations (μg/dl) were 8.3 (0.40 μmol/l) (range 1–26) for maternal prenatal, 13.4 (0.65 μmol/l) (range 4–37) for average childhood, and 8.3 (0.40 μmol/l) (range 2–33) for 6-y. The mean postnatal blood lead concentration of CLS participants increased to a peak of 17.7 (standard deviation [SD] 9.7) μg/dl (0.85 μmol/l) at 21 mo. After age 21 mo, average blood lead concentrations declined to a mean of 8.4 (SD 4.9) μg/dl (0.40 μmol/l) at 6.5 y. At 6.5 y of age, 67 children (26.9%) had a blood lead concentration above 10 μg/dl (0.48 μmol/l) (Table 1). Pearson correlations between blood lead indices examined in this study were 0.32 and 0.28 between prenatal and average childhood and 6-y respectively, and 0.80 between average childhood and 6 y.

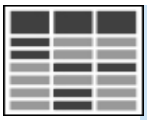


Table 1.

Characteristics of the Participants and of their Mothers in the Cincinnati Lead Study (*n* =250)

We identified a total of 800 arrests within the sample. Of these arrests, 108 (14%) were for violent offenses, 90 (11%) involved theft or fraud, 216 (28%) involved drugs, 35 (5%) were for obstruction of justice, 211 (27%) were related to serious motor vehicle offenses, 35 (5%) were for disorderly conduct, and 82 (11%) other. Approximately 55% of participants (62.8% of males, 36.3% of females) had at least one arrest. The mean number of arrests among males was 5.2, which was significantly higher than the mean number of 1.1 for females ($p < 0.001$). The overall mean arrest rate was 0.68 per year after age 18, but the mean arrest rate for males was 4.5 times higher than the female arrest rate (1.1 versus 0.25 per year).

Preliminary analysis of the association between blood lead measures and covariates revealed generally weak correlation coefficients ranging from 0.24 to 0.35, indicating a relatively small potential for confounding. In multivariable regression analyses of the total number of arrests, we found that the associations between prenatal and 6-y blood lead concentrations were statistically significant. In each model, the blood lead association was adjusted for the cofactors of maternal IQ, sex, SES score, and maternal education. The

RRs for total arrests increased for each 5 μg/dl (0.24 μmol/l) increment in blood lead concentration; the RRs were 1.40 (95% confidence interval [CI] 1.07–1.85) for prenatal blood lead, 1.07 (95% CI 0.88–1.29) for average childhood blood lead, and 1.27 (95% CI 1.03–1.57) for 6-y blood lead. The attributable risk was 0.48 arrests/year (95% CI 0.29–0.79) for prenatal blood lead, 0.13 (95% CI 0.03–0.33) for average childhood blood lead, and 0.39 (95% CI 0.21–0.68) for 6-y blood lead (Table 2). The rate of total arrests was modeled as a log-linear function of increasing blood lead concentrations for each of the three blood lead assessments: maternal prenatal (Figure 1A), early childhood (Figure 1B), and 6 y (Figure 1C).

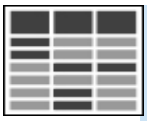


Table 2.

Relationship of Prenatal, Early Childhood Average, and Six-Year Blood Lead Concentrations with Total Arrest Rates in Young Adults

Figure 1. Adjusted Relationship between Blood Lead Concentration and Arrest Rate Ratio For Total Arrests

Shown are data for maternal prenatal blood lead concentration (A), early childhood average blood lead concentration (B), and 6-year blood lead concentration (C). Rate ratios are plotted as a function of increasing blood lead from the 5th to the 95th percentiles of blood lead relative to participants at the 5th percentile. Dashed lines are 95% confidence intervals. To convert to μmol/l: (μg/dl) × 0.04826.

In multivariable analyses of violent criminal arrests, we found statistically significant associations with both average childhood and 6-y blood lead variables. The RRs for arrests involving violent crimes increased for each 5 μg/dl (0.24 μmol/l) increment in blood lead; the RRs were1.34 (95% CI 0.88–2.03) for prenatal blood lead, 1.30 (95% CI 1.03–1.64) for average childhood blood lead, and 1.48 (95% CI 1.15–1.89) for 6-y blood lead. The attributable risk was 0.055 arrests/year (95% CI 0.026–0.118) for prenatal blood lead, 0.077 (95% CI 0.039–0.156) for average childhood blood lead, and 0.087 (95% CI 0.049–0.152) for 6-y blood lead (Table 3). As with the analyses for total arrests, the rate of arrests for violent offenses was modeled as a log-linear function of each of the blood lead indices: maternal prenatal (Figure 2A), early childhood (Figure 2B), and 6 y (Figure 2C).

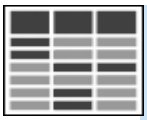


Table 3.

Relationship of Prenatal, Early Childhood Average, and Six-Year Blood Lead Concentrations with Violent Crime Arrest Rates in Young Adults

Figure 2. Adjusted Relationship between Blood Lead Concentration and Arrest Rate Ratio For Violent Offenses

Shown are data for maternal prenatal blood lead concentration (A), early childhood average blood lead concentration (B), and 6-year blood lead concentration (C). Rate ratios are plotted as a function of increasing blood lead from the 5th to the 95th percentiles of blood lead relative to participants at the 5th percentile. Dashed lines are 95% confidence intervals. To convert to μmol/l: (μg/dl) × 0.04826.

The results for analyses restricted to arrests for nonviolent crimes were similar to those found for all arrests. Specifically, the RRs for nonviolent arrests for each 5 μg/dl (0.24 μmol/l) in blood lead were 1.40 (95% CI 1.06–1.84) for prenatal blood lead, 1.05 (95% CI 0.86–1.28) for average childhood blood lead, and 1.22 (95% CI 0.97–1.53) for 6-y blood lead.

There was no statistical evidence that the shape of the exposure-response relationship differed by sex with any of the blood lead indices for total arrests or arrests for violent offenses. The interaction term for sex was statistically nonsignificant (*p*-values for interaction term ranged from 0.42 to 0.79). However, the attributable risk for males was considerably higher than for females. For example, the attributable risk for 6-y blood lead rate was 0.85 arrests/year (95% CI 0.48–1.47) for males and 0.18 (95% CI 0.09–0.33) for females.

Discussion

In a prospective birth cohort, we found that prenatal and childhood blood lead concentrations were predictors of adult arrests. Prenatal and 6-y blood lead concentrations were significantly associated with higher RRs for total arrests. Average childhood as well as later (6-y) blood lead concentrations were significantly associated with higher RRs for arrests involving a violent offense. Data from several recent prospective studies suggest

that blood lead concentrations in the later preschool years may be more predictive of cognitive and behavioral problems [23]. However, the potential importance of prenatal blood lead concentrations should not be underestimated, as they were predictive of total arrests in our data. The number of arrests in the CLS cohort was significantly higher in males. However, no significant interactions between sex and blood lead with arrest rates were found.

Environmental lead levels as well as crime have dropped over the last 30 y in the US [9]. However, the overall reduction was not uniform; inner-city children, who are predominately African-American, remain particularly vulnerable [24]. Crime and violent crime are concentrated in urban centers in the US where many poor African-Americans reside. One factor in the disproportional representation of African-Americans in crime statistics could well be the historically higher exposures to lead in these communities. Furthermore, recent data from epidemiological studies implicate blood lead concentrations well below the current level of concern adopted by the United States Centers for Disease Control in the development of neurobehavioral deficits [25]. We were unable to explore racial differences in our data since almost all participants were African-American. However, Needleman found that the lead-associated risk for juvenile court-adjudicated delinquency was present in both African-American and white youth, indicating that these findings are not restricted to any one racial or ethnic group [8].

The neurodevelopmental consequences associated with lead exposure in previous studies, such as lower IQ, less tolerance for frustration, deficits in attention, hyperactivity, and weak executive control functions, are potent predictors of delinquent and criminal behaviors [26–29]. Attention deficit hyperactivity disorder (ADHD) is a common finding among juvenile delinquents, and those with ADHD are more likely to have severe cognitive impairments [30]. ADHD is also a known risk factor for criminal behavior in adulthood [31]. A recent analysis of data from the third National Health and Nutrition Examination Survey (NHANES-III) found that higher blood lead concentrations were significantly associated with ADHD. Children with blood lead concentrations greater than 2 μg/dl were at a 4.1-fold increased risk of ADHD [32]. Similarly, in experiments with rodents, felines, and nonhuman primates, early lead exposure was associated with increased impulsivity, aggression, antagonistic interactions, reduced social play and abnormal mother–infant interaction [33–36]. Childhood lead exposure therefore seems to place individuals at risk for multiple underlying neurobehavioral deficits associated with a higher probability of later criminal behavior.

A number of mechanisms may be at work. Lead interferes with synapse formation, disrupts dopamine systems, and lowers serotonin levels. Lead exposure has been shown to reduce

MAO A (monoamine oxidase A) activity, and low MAO A activity has been associated with violent and criminal behaviors [37]. One consequence of these alterations could be neural dysfunction in areas of the brain involved in arousal, emotion, judgment, and behavioral inhibition such as the prefrontal cortex [38].

This study has several limitations. First, most criminal behavior never comes to the attention of authorities; thus, our measure of arrest underestimates actual criminal activity. Had we been able to account for all criminal acts, it is possible that the results of our study may have been different. For example, it could be argued that lead-associated lower intelligence makes it more likely that an offender will be caught (i.e., arrested). However, a recent large-scale prospective study of school-aged children with early blood lead levels similar to those in the CLS suggests that lead impacts social behaviors somewhat independently of IQ [39]. Furthermore, we did not adjust arrest rates for child IQ in our analyses because controlling for a variable that might potentially be on the causal pathway is clearly inappropriate in studies of this kind. Variables along the causal pathway between exposure and outcome cannot be bona fide confounders [40]. Second, we examined only Hamilton County, Ohio records. Although most participants in our cohort continued to reside in Hamilton County, we may have missed some arrests that occurred in other counties. Third, official records of arrest were available only when the participants reached 18 y of age. Thus, the average follow-up was under 5 y. The possibility of bias introduced by nonrandom attrition in the CLS cohort cannot be ruled out, although we found no important differences on key exposure and demographic variables. Fourth, it is always possible in observational studies to have uncontrolled confounding. This can be problematic when it comes to measuring SES, since global assessments of social standing such as the one used in this [16] and many other studies fail to capture all potentially relevant factors [41]. As pointed out by Weiss and Bellinger [42] in their discussion of the social ecology of exposure to environmental pollutants, neurotoxicant exposures are not randomly distributed, but are "chained" to many other risks to normal development that are sometimes quite difficult to partition. Finally, as with all studies of this kind, our measure of dose to the critical organ (brain) was indirect. Blood, as well as other tissues in which lead is often measured such as teeth or bone, are surrogates for dose to the central nervous system.

On the other hand, this study has a number of qualities that contribute to the validity of our findings. To our knowledge this is the first prospective study to directly examine the relationship between early exposure to lead and official documentation of arrests in adulthood. Lead dose as assessed by frequent serial blood lead determinations, assessment of a large number of potentially important covariate factors, and careful

documentation of criminal arrests were unique aspects of this investigation. Furthermore, the sample was relatively homogenous with respect to sociodemographic variables such as SES and ethnicity; thus decreasing the extent to which strong confounding factors might generate spurious associations. Therefore, we conclude that these data implicate early exposure to lead as a risk factor for behaviors leading to criminal arrest.

Acknowledgments

We are grateful to members of the Cincinnati Lead Study cohort and their families for their participation.

Author contributions. JPW, KND, MDR, and BPL designed the experiments/the study. SDW and KND collected data or did experiments for the study. RWH, MH and JPW analyzed the data. KND and SDW enrolled patients. JPW and KND wrote the first draft of the paper. JPW, KND, MDR, RWH, SDW, BPL, and MNR contributed to writing the paper.

References

1. Farrington DP (1986) Stepping stones to adult criminal careers. In: Olweus D, Block J, Radke-Yarrow M Development of Antisocial and Prosocial Behavior New York: Academic Press. pp. 359–384.
2. Farrington DP (1991) Childhood aggression and adult violence: Early precursors and later-life outcomes. Pepler DJ, Rubin KH The Development and Treatment of Childhood Aggression Hillsdale (New Jersey): Lawrence Erlbaum. pp. 5–29.
3. Nagin DS, Farrington DP (1992) The stability of criminal potential from childhood to adulthood. Criminology 30: 235–260. **FIND THIS ARTICLE ONLINE**
4. Lipsy MW, Derzon JH (1998) Predictors of violent or serious delinquency in adolescence and early adulthood: a synthesis of longitudinal research. In: Loeber R, Farrington DP Serious and Violent Juvenile Offenders: Risk Factors and Successful Interventions Thousand Oaks (California): Sage Publications. pp. 86–105.
5. Denno D (1990) Biology and Violence New York: Cambridge University Press.
6. Needleman HL, Riess JA, Tobin MJ, Biesecker GE, Greenhouse JB (1996) Bone lead levels and delinquent behavior. JAMA 275: 363–369. **FIND THIS ARTICLE ONLINE**
7. Dietrich KN, Ris MD, Succop PA, Berger OG, Bornschein RL (2001) Early exposure to lead and juvenile delinquency. Neurotoxicol Teratol 23: 511–518. **FIND THIS ARTICLE ONLINE**
8. Needleman HL, McFarland C, Ness RB, Fienberg SE, Tobin MJ (2002) Bone lead levels in adjudicated delinquents: a case control study. Neurotoxicol Teratol 24: 711–717. **FIND THIS ARTICLE ONLINE**
9. Nevin R (2000) How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. Environ Res 83: 1–22. **FIND THIS ARTICLE ONLINE**
10. Nevin R (2007) Understanding international crime trends: The legacy of preschool lead exposure. Environ Res 104: 315–336. **FIND THIS ARTICLE ONLINE**

11. Stretesky PB, Lynch MJ (2001) The relationship between lead exposure and homicide. Pedatr Adol Med 155: 579–582. **FIND THIS ARTICLE ONLINE**
12. Masters RD, Hone B, Doshi A (1997) Environmental pollution, neurotoxicity, and criminal behavior. In: Rose J Aspects of environmental toxicology London: Taylor and Francis Group. pp. 13–48.
13. Clark CS, Bornschein RL, Succop P, Que Hee SS, Hammond PB, Peace B (1985) Condition and type of housing as an indicator of potential environmental lead exposure and pediatric blood lead levels. Environ Res 38: 46–53. **FIND THIS ARTICLE ONLINE**
14. Dietrich KN, Krafft KM, Borschein RL, Hammond PB, Berger O, et al. (1987) Low level fetal lead exposure effect on neurobehavioral development in early infancy. Pediatrics 80: 721–730. **FIND THIS ARTICLE ONLINE**
15. Dietrich KN, Berger OG, Succop PA, Hammond PB, Bornschein RL (1993) The developmental consequences of low to moderate prenatal and postnatal lead exposure: intellectual attainment in the Cincinnati Lead Study Cohort following school entry. Neurotoxicol Teratol 15: 37–44. **FIND THIS ARTICLE ONLINE**
16. Cirino PT, Chin CE, Sevcik RA, Wolf M, Lovett M, et al. (2002) Measuring socioeconomic status: reliability and preliminary validity for different approaches. Assessment 9: 145–155. **FIND THIS ARTICLE ONLINE**
17. Bradley RH, Caldwell BM (1979) Home observation for measurement of the environment: a revision of the preschool scale. Am J Mental Defic 84: 235–244. **FIND THIS ARTICLE ONLINE**
18. Cameron AC, Trivedi PK (1998) Regression analysis of count data Cambridge (United Kingdom): University of Cambridge Press.
19. Silverstein AB (1985) Two-and four-subtest short forms of the WAIS-R: a closer look at validity and reliability. J Clin Psychol 41: 95–97. **FIND THIS ARTICLE ONLINE**
20. Moffitt TE, Caspi A, Rutter M, Silva PA (2003) Sex differences in antisocial behavior: conduct disorder, delinquency, and violence in the Dunedin Longitudinal Study Cambridge (United Kingdom): University of Cambridge Press.
21. Bellsley DA, Kuh E, Welsch RE (1980) Regression diagnostics New York: Wiley.
22. SAS (2004) Statistical analysis system, version 9.1 Cary, North Carolina: SAS Institute.
23. Chen A, Dietrich KN, Ware JH, Radcliffe J, Rogan WJ (2005) IQ and blood lead from 2 to 7 years of age: are the effects in older children the residual of high blood lead concentrations in 2-year-olds. Environ Health Perspect 113: 597–601. **FIND THIS ARTICLE ONLINE**
24. Pirkle JL, Kaufmann RB, Bordy DJ, Hickman T, Gunter EW, et al. (1998) Exposure of the U.S. population to lead, 1991–1994. Environ Health Perspect 106: 745–750. **FIND THIS ARTICLE ONLINE**
25. Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, et al. (2005) Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ Health Perspect 113: 894–899. **FIND THIS ARTICLE ONLINE**

26. Silva PA, Hughes P, Williams S, Faed JM (1988) Blood lead, intelligence, reading attainment, and behaviour in eleven year old children in Dunedin, New Zeland. New Zealand. J Child Psychol Psychiatry Allied Discip 29: 43–52.
27. Thomson GOB, Raab GM, Hepburn WS, Hunter R, Fulton M, Laxen DHP (1989) Blood-lead levels and children behavior—results from the Edinburgh lead study. J. Child Psychol. Psychiatry 30: 515–528.
28. Fergusson DM, Fergusson JE, Horwood LJ, Kinzett NG (1988) A longitudinal study of dentine lead levels, intelligence, school performance and behaviour. Part III. Dentine lead levels and attention/activity. J Child Psychol Psychiatry Allied Discip 29: 811–824.
29. Canfield RL, Kreher DA, Cornwell C, Herderson CR (2003) Low-level lead exposure, executive functioning, and learning in early childhood. Child Neuropsychol 9: 35–43.
30. Moffitt TE, Silva PA (1988) Self-reported delinquency, neuropsychological deficit, and history of attention deficit disorder. J Abnorm Child Psychol 16: 553–569.
31. Vitelli R (1996) Prevalence of childhood conduct disorder and attention-deficit hyperactivity disorders in adult maximum-security inmates. Int J Offender Therapy Compar Criminol 40: 263–271.
32. Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP (2006) Exposures to environmental toxicants and attention deficit hyperactivity disorder in US children. Environ Health Perspect 114: 1904–1909.
33. Cory-Slechta DA (2003) Lead-induced impairments in complex cognitive function: Offerings from experimental studies. Child Neuropsychol 9: 54–75.
34. Delville Y (1999) Exposure to lead during development alters aggressive behavior in golden hamsters. Neurotoxicol Teratol 21: 445–449.
35. Li W, Han S, Gregg TR, Kemp FW, Davidow AL, et al. (2003) Lead exposure potentiates predatory attack behavior in the cat. Environ Res 92: 197–206.
36. Laughlin NK, Bushnell PJ, Bowman RE (1991) Lead exposure and diet: Differential effects on social development in the rhesus monkey. Neurotoxicol Teratol 13: 429–440.
37. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, et al. (2002) Role of genotype in the cycle of violence in maltreated children. Science 297: 851–854.
38. Lidsky T, Schneider JS (2003) Lead neurotoxicity in children: Basic mechanisms and clinical correlates. Brain 126: 5–19.
39. Chen A, Cai B, Dietrich KN, Radcliffe J, Rogan WJ (2007) Lead exposure, IQ, and behavior in urban 5- to 7-year-olds: Does lead affect behavior only by lowering IQ. Pediatrics 119: 650–658.
40. Jacobson JL, Jacobson SW (1996) Prospective longitudinal assessment of developmental neurotoxicity. Environ Health Perspect 104(Suppl 2): 275–283.
41. Braverman PA, Cubbin C, Egerter S, Chideya S, Marchi KS, et al. (2005) Socioeconomic status in health research. One size does not fit all. JAMA 294: 2879–2888.
42. Weiss B, Bellinger DC (2006) Social ecology of children's vulnerability to environmental pollutants. Environ Health Perspect 114: 1479–1485.

Environmental Health Perspective
Volume 113, Number 7, July 2005
Research | Children's Health

Low-Level Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis

Bruce P. Lanphear,[1,2] Richard Hornung,[1,2,3] Jane Khoury,[1,2] Kimberly Yolton,[1] Peter Baghurst,[4] David C. Bellinger,[5] Richard L. Canfield,[6] Kim N. Dietrich,[1,2] Robert Bornschein,[2] Tom Greene,[7] Stephen J. Rothenberg,[8,9] Herbert L. Needleman,[10] Lourdes Schnaas,[11] Gail Wasserman,[12] Joseph Graziano,[13] and Russell Roberts[14]

[1]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [2]Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA; [3]Institute for Health Policy and Health Services Research, Department of Environmental Health, University of Cincinnati, Cincinnati, Ohio, USA; [4]Women and Children's Hospital, North Adelaide, South Australia; [5]Department of Neurology, Children's Hospital Boston and Harvard Medical School, Boston, Massachusetts, USA; [6]Division of Nutritional Sciences, Cornell University, Ithaca, New York, USA; [7]Department of Biostatistics and Epidemiology, Cleveland Clinic Foundation, Cleveland, Ohio, USA; [8]Center for Research in Population Health, National Institute of Public Health, Cuernavaca, Morelos, Mexico; [9]Drew University, Los Angeles, California, USA; [10]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA; [11]National Institute of Perinatology, Mexico City, Mexico; [12]Department of Child Psychiatry, Columbia University, New York, New York, USA; [13]Department of Environmental Health Sciences, Columbia University, New York, New York, USA; [14]School of Applied Psychology, Griffith University, Queensland, Australia

Abstract

Lead is a confirmed neurotoxin, but questions remain about lead-associated intellectual deficits at blood lead levels < 10 µg/dL and whether lower exposures are, for a given change in exposure, associated with greater deficits. The objective of this study was to examine the association of intelligence test scores and blood lead concentration, especially for children who had maximal measured blood lead levels < 10 µg/dL. We examined data collected from 1,333 children who participated in seven international population-based longitudinal cohort studies, followed from birth or infancy until 5-10 years of age. The full-scale IQ score was the primary outcome measure. The geometric mean blood lead concentration of the children peaked at 17.8 µg/dL and declined to 9.4 µg/dL by 5-7 years of age ; 244 (18%) children had a maximal blood lead concentration < 10 µg/dL, and 103 (8%) had a maximal blood lead concentration < 7.5 µg/dL. After adjustment for covariates, we found an inverse relationship between blood lead concentration and IQ score. Using a log-linear model, we found a 6.9 IQ point decrement [95% confidence interval (CI) , 4.2-9.4] associated with an increase in concurrent blood lead levels from 2.4 to 30 µg/dL. The estimated IQ point decrements associated with an increase in blood lead from 2.4 to 10 µg/dL, 10 to 20 µg/dL, and 20 to 30 µg/dL were 3.9 (95% CI, 2.4-5.3) , 1.9 (95% CI, 1.2-2.6) , and 1.1 (95% CI, 0.7-1.5) , respectively. For a given increase in blood lead, the lead-associated intellectual decrement for children with a maximal blood lead level < 7.5 µg/dL was significantly greater than that observed for those with a maximal blood lead level ≥ 7.5 µg/dL ($p = 0.015$) . We conclude that environmental lead exposure in children who have maximal blood lead levels < 7.5 µg/dL is associated with intellectual deficits. *Key words:* blood lead concentration, children, environment, epidemiology, intelligence, lead, lead toxicity. *Environmental Health Perspective* 113: 894-899 (2005) . doi:10.1289/ehp.7688 available via *http://dx.doi.org/* [Online 18 March 2005]

Environmental Health Perspective
Volume 114, Number 12, December 2006

Exposures to Environmental Toxicants and Attention Deficit Hyperactivity Disorder in U.S. Children

Joe M. Braun,[1] Robert S. Kahn,[2,3] Tanya Froehlich,[3,4] Peggy Auinger,[5] and Bruce P. Lanphear[2,3]

[1]College of Nursing, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin, USA; [2]Division of General and Community Pediatrics, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [3]Cincinnati Children's Environmental Health Center, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [4]Division of Developmental Behavioral Pediatrics, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [5]Department of Pediatrics, University of Rochester School of Medicine, Rochester, New York, USA

Abstract

Objective: The purpose of this study was to examine the association of exposures to tobacco smoke and environmental lead with attention deficit hyperactivity disorder (ADHD) .

Methods: Data were obtained from the National Health and Nutrition Examination Survey 1999–2002. Prenatal and postnatal tobacco exposure was based on parent report ; lead exposure was measured using blood lead concentration. ADHD was defined as having current stimulant medication use and parent report of ADHD diagnosed by a doctor or health professional.

Results: Of 4,704 children 4–15 years of age, 4.2% were reported to have ADHD and stimulant medication use, equivalent to 1.8 million children in the United States. In multivariable analysis, prenatal tobacco exposure [odds ratio (OR) = 2.5 ; 95% confidence interval (CI) , 1.2–5.2] and higher blood lead concentration (first vs. fifth quintile, OR = 4.1 ; 95% CI, 1.2–14.0) were significantly associated with ADHD. Postnatal tobacco smoke exposure was not associated with ADHD (OR = 0.6 ; 95% CI, 0.3–1.3 ; p = 0.22) . If causally linked, these data suggest that prenatal tobacco exposure accounts for 270,000 excess cases of ADHD, and lead exposure accounts for 290,000 excess cases of ADHD in U.S. children.

Conclusions: We conclude that exposure to prenatal tobacco and environmental lead are risk factors for ADHD in U.S. children.

Key words: ADHD, attention deficit hyperactivity disorder, blood lead, children, environmental tobacco smoke, lead poisoning, NHANES, prenatal tobacco exposure, tobacco. *Environmental Health Perspective* 114:1904–1909 (2006) . doi:10.1289/ehp.9478 available via *http://dx.doi.org/* [Online 19 September 2006]

Address correspondence to B.P. Lanphear, Mail location 7035, 2800 Winslow Ave., Cincinnati OH 45206 USA. Telephone: (513) 636-3778. Fax: (513) 636-4402. E-mail: bruce.lanphear@cchmc.org

This research was supported by grants from the National Institute of Child Health and Human Development HD40362 (R.S.K.) , HD41141 (R.S.K.) , National Research Service Award 1T32PE10027 (T.F.) , National Institutes of Health and U.S. Environmental Protection Agency PO1-ES11261 (B.P.L.) .

The authors declare they have no competing financial interests. Received 1 July 2006 ; accepted 18 September 2006.

The NEW ENGLAND JOURNAL of MEDICINE

Established in 1812 April 17 , 2003, Vol. 348, Number 16

Intellectual Impairment in Children with Blood Lead Concentrations below 10 µg per Deciliter

Richard L. Canfield, Ph.D., Charles R. Henderson, Jr., M.A.,
Deborah A. Cory-Slechta, Ph.D., Christopher Cox, Ph.D., Todd A. Jusko, B.S.,
and Bruce P. Lanphear, M.D., M.P.H.

ABSTRACT

BACKGROUND:
Despite dramatic declines in children's blood lead concentrations and a lowering of the Centers for Disease Control and Prevention's level of concern to 10 µg per deciliter (0.483 µmol per liter), little is known about children's neurobehavioral functioning at lead concentrations below this level.

METHODS:
We measured blood lead concentrations in 172 children at 6, 12, 18, 24, 36, 48, and 60 months of age and administered the Stanford–Binet Intelligence Scale at the ages of 3 and 5 years. The relation between IQ and blood lead concentration was estimated with the use of linear and nonlinear mixed models, with adjustment for maternal IQ, quality of the home environment, and other potential confounders.

RESULTS:
The blood lead concentration was inversely and significantly associated with IQ. In the linear model, each increase of 10 µg per deciliter in the lifetime average blood lead concentration was associated with a 4.6-point decrease in IQ (P=0.004), whereas for the subsample of 101 children whose maximal lead concentrations remained below 10 µg per deciliter, the change in IQ associated with a given change in lead concentration was greater. When estimated in a nonlinear model with the full sample, IQ declined by 7.4 points as lifetime average blood lead concentrations increased from 1 to 10 µg per deciliter.

CONCLUSIONS:
Blood lead concentrations, even those below 10 µg per deciliter, are inversely associated with children's IQ scores at three and five years of age, and associated declines in IQ are greater at these concentrations than at higher concentrations. These findings suggest that more U.S. children may be adversely affected by environmental lead than previously estimated.

Source Information:

From the Division of Nutritional Sciences (R.L.C.) and the Department of Human Development (C.R.H.), College of Human Ecology, Cornell University, Ithaca, N.Y.; the Departments of Environmental Medicine (D.A.C.-S.) and Biostatistics and Computational Biology (C.C.), University of Rochester School of Medicine, Rochester, N.Y.; the Division of Epidemiology, Statistics, and Prevention, National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, Bethesda, Md. (C.C.); the Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle (T.A.J.); and Cincinnati Children's Environmental Health Center, Children's Hospital Medical Center, Cincinnati (B.P.L.).

CURRICULUM VITAE

Bruce Perrin Lanphear, M.D., M.P.H.

Work
Division of General & Community Pediatrics
Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, Ohio 45229-3039
TEL: (513) - 636 - 3778
FAX: (513) - 636 - 4402
E-mail: bruce.lanphear@chmcc.org

Home
3526 Mooney
Cincinnati, OH 45208
TEL: (513) 321-1927
Cell: (513) 708-3939

Date of Birth: January 12th, 1963

Marital status: Married to Nancy Lanphear, M.D., a developmental pediatrician

Children: Three children, Rachel (15), Ella (10) and Martha (8)

Specialty

Board certified in General Preventive Medicine & Public Health

Employment

1984-86	Paramedic, Jackson County Jail, Kansas City, Missouri
1988-89	Physician, International Travel Clinic, University of Cincinnati, Cincinnati, Ohio
1988-89	Staff Physician, Sexually Transmitted Disease Clinic, Cincinnati Public Health Department, Cincinnati, Ohio
1989-92	Assistant Professor of Environmental Health, Associate Director, Medical Center Health Services, University of Cincinnati
1992-94	Senior Instructor, Departments of Pediatrics and of Community & Preventive Medicine, University of Rochester School of Medicine.
1992-95	National Research Scholar Award in General Pediatric Research, University of Rochester School of Medicine and Dentistry.
1992-1997	Course Director, "Public Health & the Environment", Department of Community & Preventive Medicine, The University of Rochester School of Medicine and Dentistry.
1992-1997	Assistant Professor, Department of Pediatrics and of Community & Preventive Medicine, University of Rochester School of Medicine.
1997-2002	Associate Professor, Department of Pediatrics, Children's Hospital Medical Center and the University of Cincinnati, Cincinnati, Ohio.
1997-	Director, General Pediatric Research Fellowship Training Program, Children's Hospital Medical Center and the University of Cincinnati.
1997-	Director, Children's Environmental Health Center, Children's Hospital Medical Center and the University of Cincinnati.
1997-	Associate Professor (Adjunct), Departments of Pediatrics and of Environmental Medicine, University of Rochester School of Medicine & Dentistry, Rochester, NY.
1998-2003	Associate Director for Research, Division of General & Community Pediatrics, Children's Hospital Medical Center.
2001-	Associate Professor (tenured), Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio.
2001-	Associate Professor (Adjunct), Department of Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, Michigan.
2002-	The Sloan Professor of Children's Environmental Health, Departments of Pediatrics and Environmental Health, University of Cincinnati, Cincinnati, Ohio.

Education

1980-86	University of Missouri at Kansas City Medical Degree (1986)
1986-87	Transitional Internship, University of Arkansas for Medical Sciences, Little Rock, Arkansas.
1987-88	Tulane School of Public Health & Tropical Medicine Masters in Public Health & Tropical Medicine.
1987-89	General Preventive Medicine and Public Health Residency Tulane School of Public Health & Tropical Medicine
1992-95	Fellowship in General Academic Pediatric Research University of Rochester School of Medicine, Rochester, NY

Committee and Community Involvement

1993-1997	Lead Poisoning Prevention Task Force, Monroe County Health Department.
1994-1997	Investigational Review Board, Rochester General Hospital.
1995-	Scientific Consultant, National Center for Lead-Safe Housing, Columbia, Maryland.
1996-1997	Member, New York State Task Force on Environmental Neurotoxins, University of Rochester School of Medicine.
1996-2001	Member, National Institute for Environmental Health Sciences Grant Review Committee for Community-Based Interventions.
1996-1998	Chairman, U.S. Department of Housing and Urban Development Committee on Lead-Contaminated House Dust.
1996-	Scientific Consultant, Westat, Inc., Rockville, Maryland.
1998	Member, Review Group for National Research Service Awards, Health Resources and Services Administration.
1998-2000	Member, Cincinnati Board of Health, Cincinnati, Ohio.
1998-2001	Member, Science and Research Work Group, Office of Children's Health Protection Advisory Committee, U.S. EPA.
1998-2000	Member, Cincinnati Lead Poisoning Prevention Advisory Task Force, Cincinnati, Ohio.
1998-	Scientific Consultant, Battelle Memorial Institute, Columbus, Ohio.
1997-	Research Scholar, Institute for Health Policy and Health Services Research, University of Cincinnati, Cincinnati, Ohio.
1999	Member, K23 Grant Review Committee, National Institute for Environmental Health Sciences, August 1999.
1999	Member, Expert Panel on Soil Pica Behavior, Agency for Toxic Substance Disease Registry, June 7th-8th, Atlanta, Georgia.
2000	Member, Panel on Health Disparities: Linking Biological and Behavioral Mechanisms with Social and Physical Environments, National Institute for Environmental Health Sciences, July 14-15th.
2000-	Scientific Consultant, Abt Associates, Rockville, Maryland.
2000-02	Member, Workshop on Assessing Environmental Exposures to Children, U.S. Environmental Protection Agency, July 26-27th.
2000-04	Member, Children's Environmental Health Project, AAP's Child Health Research Center, Rochester, NY.
2001	Participant, "ILSI Workshop to Develop a Framework for Assessing Risks to Children from Exposure to Environmental Agents", Stowe, Vermont, July 30 to August 2nd 2001.
2001	Senate Testimony, "Ensuring that Children with Dangerous Levels of Lead in their Blood Receive Care as Early as Possible". Subcommittee on Housing and Transportation of the Committee on Banking, Housing and Urban Affairs, 107th U.S. Congress, November 13th, 2001.
2001	Reviewer, National Research Council, National Academy of Science Update of the 1999 Arsenic in Drinking Water Report.
2001-2003	Member, Expert Panel on Children's Health and the Environment, North American Commission for Environmental Cooperation.
2002	Member, Scientific Advisory Board, Scientist Communication Network.
2003	Member, "Herculaneum Health Study Workshop" Agency for Toxic Substance Diseases Registry, May 22nd to 23rd, 2003.

2003-2004 Panel Member, "Lead Poisoning in Pregnant Women", Mt. Sinai for Children's Health and the Environment, New York, NY.

2003 Member, "Invitational Workshop on a proposed American Family Study" National Human Genome Research Institute, December 1st to 3rd, 2003.

2004-2006 Member, Committee on "Ethical Consideration for Research on Housing-Related Health-Hazards involving Children". National Research Council and the Institute of Medicine, The National Academies.

2004 Congressional Testimony, "Tapped Out? Lead in the District of Columbia and the Providing of Safe Drinking Water". Subcommittee on Environment and Hazardous Materials of the Committee on Energy and Commerce, U.S. House of Representatives, 108th Congress, July 22nd, 2004.

2005 Reviewer, "Superfund and Mining Megasites – Lessons from the Couer d" Alene River Basin". National Research Council, The National Academies.

2005 Ad Hoc Member, NIEHS Board of Scientific Counselors Review of the Epidemiology Branch, April 3rd to April 5th, 2005.

2005 Senate Briefing, "The Connection of Environmental Chemicals and Learning Disabilities", The Relationship Between Chemical Exposures and Incidence of Learning and Other Developmental Disabilities, U.S. Senate, May 10th, 2005.

2006 Invited Participant, NIEHS Strategic Planning Forum, National Institute for Environmental Health Sciences, Chapel Hill, North Carolina, October 17-18th, 2006.

2006- Member, U.S. EPA's Clean Air Scientific Advisory Committee Lead Review Panel.

2006- Member, National Children's Study Steering Committee

2006 Invited Participant, "How Does Housing Affect Health Outcomes of Children?", MacArthur Foundation, Chicago, Illinois, June 21st-22nd, 2006.

2006- Member, External Scientific Advisory Committee, Richmond Center for Excellence in Tobacco Research, American Academy of Pediatrics.

2007 Testimony, Vermont State Legislature, "The Lingering Legacy of Lead Toxicity", Montpelier, Vermont, February 1st, 2007.

Editorial Boards

2000- Assistant Editor, *Environmental Research*

2000- Deputy Editor, *Public Health Reports*

2004 Associate Editor, *Pediatrics* supplement on Children's Environmental Health

2004- Editorial Board Member, *PLoS Medicine*

2005- Editorial Board Member, *Breastfeeding Medicine*

Societies and Organizations

1989- American Public Health Association

1989- Association of Teachers of Preventive Medicine

1996- Ambulatory Pediatric Association

1997- American Association for the Advancement of Science

2000- Society for Pediatric Research

2001- American Pediatric Society

2001- Specialty Fellow, American Academy of Pediatrics

2006 Fellow, Collegium Ramazzini

Original Research

1. Lanphear BP. Deaths in Custody. American Journal Forensic Medicine & Pathology 1987;8:299-301.

2. Lanphear BP, Snider DE. Myths of Tuberculosis. J Occ Med 1991;33:501-504.
3. Linnemann CC Jr, Cannon C, DeRonde M, Lanphear BP. Effect of educational programs, rigid sharps containers, and universal precautions on reported needle-stick injuries in healthcare workers. Infection Control Hospital Epidemiology 1991;12:214-20.
4. Lanphear BP, Buncher CR. Latent period for malignant mesothelioma of occupational origin. Journal Occupational Med 1992;34:718-721.
5. Lanphear BP, Linnemann CC Jr, Cannon CG, DeRonde MM. Decline of clinical hepatitis B in workers at a general hospital. Clinical Infectious Disease 1993:11:10-14.
6. Lanphear BP, Linnemann CC Jr, Cannon C, DeRonde MM, Pendy L, Kerly L. Hepatitis C virus infection in health care workers. Infection Control Hospital Epidemiology 1994;15:745-750.
7. Lanphear BP, Emond M, Jacobs DE, Weitzman M, Winter NL, Tanner M, Yakir B, Eberly S. A side-by-side comparison of dust collection methods for sampling lead-contaminated house-dust. Environmental Research 1995;68:114-123.
8. Lanphear BP, Winter NL, Apetz L, Eberly S, Weitzman M. A randomized trial of the effect of dust control on children's blood lead levels. Pediatrics 1996;98:35-40.
9. Christy C, Pulcino M, Lanphear BP, McConnochie K. Screening for tuberculosis infection in urban children. Arch Pediatrics Adolescent Med 1996;150:722-726.
10. Lanphear BP, Weitzman M, Eberly S. Racial differences in environmental exposures to lead. American Journal of Public Health 1996;86:1460-1463.
11. Lanphear BP, Weitzman M, Winter NL, Tanner M, Yakir B, Eberly S, Emond M, Matte TD. Lead-contaminated house dust and urban children's blood lead levels. American Journal of Public Health 1996;86:1416-1421.
12. Lanphear BP, Byrd RS, Auinger P, Hall CB. Increasing prevalence of recurrent otitis media among children in the United States. Pediatrics 1997 http//www.pediatrics.org/cgi/contents/full99/3/e1.
13. Emond MJ, Lanphear BP, Watts A, Eberly S for the Rochester Lead-in-Dust Study Group. Measurement error and its impact on the estimated relationship between dust lead and children's blood lead. Environmental Research 1997;72:82-92.
14. Lanphear BP, le Cessie S, Atkinson WL, Watelet L. Association of live births and the resurgence of measles. International Journal Epidemiology 1997;26:204-211.
15. Rust SW, Burgoon DA, Lanphear BP, Eberly S. Log-additive versus log-linear analysis of lead-contaminated house dust and children's blood lead levels: Implications for residential dust-lead standard. Environmental Research 1997;72:173-184.
16. Lanphear BP, Roghmann KJ. Pathways of lead exposure in urban children. Environmental Research 1997;74:67-73.
17. Lanphear BP, Byrd RS, Auinger P, Schaffer S. Community characteristics associated with elevated blood lead levels in children. Pediatrics 1998;101:264-271.
18. Lanphear BP, Rust SW, Burgoon DA, Eberly S, Galke W. Environmental exposures to lead and urban children's blood lead levels. Environmental Research 1998;76:120-130.
19. Lanphear BP. The paradox of lead poisoning prevention. Science 1998;281:1617-1618.

20. Lanphear BP, Hall CB, Black J, Auinger P. Risk factors for the early acquisition of HHV-6 and HHV-7 infection in children. Pediatric Infectious Disease Journal 1998;17:792-795.
21. Lanphear BP, Matte TD, Rogers J, Clickner R, Dietz B, Bornschein RL, Succop P, Mahaffey KR, Dixon S, Galke W, Rabinowitz M, Farfel M, Rohde C, Schwartz J, Ashley P and Jacobs DE. The contribution of lead-contaminated house dust and residential soil to children's blood lead levels: A pooled analysis of 12 epidemiologic studies. Environmental Research 1998;79:51-68.
22. Marron R, Lanphear BP, Kouides R, Dudman L, Manchester R, Christy C. Efficacy of informational letters on Hepatitis B immunization rates in university students. J Am College Health 1998;47:123-127.
23. Howard CR, Howard FM, Lanphear BP, deBlieck EA, Eberly S, Lawrence RA. Effect of early pacifier use on breastfeeding duration. Pediatrics 1999;103:http//www.pediatrics.org/cgi/contents/full103/3/e33.
24. Lanphear BP, Howard CR, Eberly S, Auinger P, Kolassa J, Weitzman M, Alexander K, Schaffer S. Primary prevention of childhood lead exposure: A randomized trial of dust control. Pediatrics 1999;103:772-777.
25. Moss ME, Lanphear BP, Auinger P. Association of dental caries and blood lead levels among the U.S. population. JAMA 1999;281:2294-2298.
26. Howard CR, de Blieck EA, ten Hoopen C, Howard F, Lanphear BP, Lawrence RA. Physiologic stability of newborns during cup and bottle-feeding. Pediatrics 1999;104:1204-1207.
27. Steiner JF, Curtis P, Lanphear BP, Vu KO, Reid A. Federally-funded fellowship training in primary care research: perspectives of program directors. Academic Medicine 2000;75:74-80.
28. Stone KE, Lanphear BP, Pomerantz WJ, Khoury J. Injuries and deaths in children due to window-falls. Journal of Urban Health 2000;77:26-33.
29. Mansour M, Lanphear BP, DeWitt TG. Barriers to asthma care among underserved, urban children. Pediatrics 2000;106:512-519.
30. Lanphear BP, Eberly S, Howard CR. Long-term effect of dust control on children's blood lead levels. Pediatrics 2000 http//www.pediatrics.org/cgi/contents/full106/4/e48.
31. Lanphear BP, Dietrich KN, Auinger P, Cox C. Cognitive deficits associated with blood lead levels <10 μg/dl in U.S. children and adolescents. Public Health Reports 2000;115:521-529.
32. Lanphear BP, Aligne C, Auinger P, Byrd R, Weitzman M. Residential exposures associated with asthma in U.S. children. Pediatrics 2001;107:505-511.
33. Lanphear BP, Kahn RS, Berger O, Auinger P, Bortnick S, Naahas R. Contribution of residential exposures to asthma in US children and adolescents. Pediatrics 2001 http://www.pediatrics.org/cgi/content/full/107/6/e98.
34. Phelan KJ, Kalkwarf H, Khoury J, Lanphear BP. Trends and patterns of playground injuries in U.S. children and adolescents. Ambulatory Pediatrics 2001;1:227-233.
35. Mansour M, Lanphear BP, Hornung R, Khoury J, Bernstein DI, Menrath W, Decolongon J. A side-by-side comparison of sampling methods for settled indoor allergens. Environ Res 2001;87:37-46.
36. Haynes E, Lanphear BP, Tohn E, Farr N, Rhoads GG. The effect of dust control on children's blood lead concentrations: A systematic review. Env Health Perspect 2002;110:103-107.

37. Lanphear BP, Hornung R, Ho M, Howard CR, Eberly S, Knauf K. Environmental lead exposure during early childhood. Journal of Pediatrics 2002;140:40-47.
38. Steiner JF, Lanphear BP, Curtis P, Vu KO. The training and career paths of fellows in the National Research Service Award (NRSA) program for research in primary medical care. Acad Med 2002;77:712-718.
39. Steiner JF, Lanphear BP, Curtis P, Vu KO. Indicators of early research productivity among primary care fellows. J Gen Intern Med 2002;17:845-851.
40. Kalkwarf HJ, Khoury JC, Lanphear BP. Milk intake in childhood and adolescence, adult bone density and osteoporotic fractures in U.S. women. Am J Clin Nut 2003;77:257-265.
41. Howard CR, Howard FM, Lanphear BP, Eberly S, deBlieck EA, Oakes D, Lawrence RA. A randomized trial of pacifier use and bottle-feeding and their effect on breastfeeding. Pediatrics 2003;111:511-518.
42. Curtis P, Dickinson P, Steiner J, Lanphear BP, Vu K. Building capacity for research in family medicine: Is the blueprint faulty? Family Medicine 2003;35:124-130.
43. Lanphear BP, Succop P, Roda S, Henningsen G. The Effect of Soil Abatement on Blood Lead Levels in Children living near a Former Smelting and Milling Operation. Public Health Reports 2003;118:83-90.
44. Canfield RL, Henderson CR, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 micrograms per deciliter. N Engl J Med 2003;348:1517-1526.
45. Kahn RS, Khoury JC, Nichols WC, Lanphear BP. Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactivity-impulsivity, inattentive and oppositional behaviors. Journal of Pediatrics 2003:143: 104-110.
46. Auinger P, Kalkwarf HJ, Mansour M, Lanphear BP. Trends in Otitis Media in US Children. Pediatrics 2003:112:514-520.
47. Haynes E, Kalkwarf H, Hornung R, Wenstrup R, Dietrich K, Lanphear BP. Vitamin D Fok1 polymorphism and blood lead concentration in children. Environ Health Persp 2003;111:1665-1669.
48. Steiner JF, Curtis P, Lanphear BP, Vu KO, Main DS. Assessing the role of influential mentors in the research development of primary care fellows. Academic Medicine 2004:79:865-872.
49. Yolton K, Auinger P, Dietrich KN, Lanphear BP, Hornung R. Exposure to environmental tobacco smoke and cognitive abilities among US children and adolescents. Environ Health Persp 2005:113:98-103.
50. Phelan KJ, Khoury J, Kalkwarf H, Lanphear BP. Residential injuries in US children and adolescents. Public Health Reports 2005;120:63-70.
51. Wilson SE, Kahn RS, Khoury J, Lanphear BP. Racial differences in exposure to environmental tobacco smoke among children. Environ Health Perspect 2005;113:362-367.
52. Lanphear BP, Hornung R, Ho M. Screening housing to prevent lead toxicity in children. Pub Health Rep 2005;120:305-310.
53. Rosner D, Markowitz G, Lanphear BP. J. Lockhart Gibson and the discovery of the impact of lead pigments on children's health: A review of a century of knowledge. Pub Health Rep 2005;120:296-300.
54. Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, Canfield RL, Dietrich KN, Bornschein R, Greene T, Rothenberg SJ, Needleman HL, Schnaas L, Wasserman G, Graziano J. Low-

level environmental lead exposure and children's intellectual function: An international pooled analysis. Environ Health Perspect 2005;113:894-899.

55. Nagaraja J, Menkedick J, Phelan KJ, Ashley PJ, Zhang J, Lanphear BP. Deaths from residential injuries in US children and adolescents, 1985 to 1997. Pediatrics 2005;116:454-61.
56. Eskenazi B, Gladstone EA, Berkowitz GS, Drew CH, Faustman EM, Holland NT, Lanphear BP, Meisel SJ, Perera FP, Rauh VA, Sweeney A, Whyatt RM, Yolton K. Methodologic and logistic issues in conducting longitudinal birth cohort studies: Lessons learned from the Centers for Children's Environmental Health and Disease Prevention Research. Environ Health Persp 2005;113:1419-1429.
57. Eggleston PA, Diette G, Lipsett M, Lewis T, Tager I, McConnell R, Chrischilles E, Lanphear BP, Miller R, Krishnan J. Lessons learned for the study of childhood asthma from the Centers for Children's Environmental Health and Disease Prevention Research. Environ Health Persp 2005;113:1430-1436.
58. Spanier, AJ, Hornung, R, Lierl, M, and Lanphear, B. Environmental exposures and exhaled nitric oxide in children with asthma. Journal of Pediatrics 2006;149:220-226.
59. Yuan W, Holland S, Cecil K, Dietrich K, Wessel SD, Altaye M, Hornung R, Ris M, Egelhoff J, Lanphear B. The impact of early childhood lead exposure on brain organization: A functional magnetic resonance imaging study of language function. Pediatrics 2006;118:971-977.
60. Howard CR, Lanphear NE, Lanphear BP, Eberly S, Lawrence RA. Parental Responses to Infant Crying and Colic: The Effect on Breastfeeding Duration. Breastfeeding Medicine 2006;3:146-155.
61. Brinkman W, Geraghty S, Lanphear B, Khoury J, Gonzalez-Del-Rey J, DeWitt T, Britto M. Evaluation of resident communication skills and professionalism: A matter of perspective? Pediatrics 2006;118:1371-1379.
62. Brinkman W, Geraghty S, Lanphear B, Khoury J, Gonzalez-Del-Rey J, DeWitt T, Britto M. Impact of multi-source feedback on resident communication skills and professionalism. Arch Ped Adolesc Med 2007;161:44-49.
63. Braun J, Kahn RS, Froehlich T, Auinger P, Lanphear BP. Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. Environ Health Perspect 2006;114:1904-1909.
64. Froehlich T, Lanphear BP, Dietrich KN, Cory-Slechta D, Wang N, Kahn RS. ADHD-related Executive Function: Interactions of the DRD4 Polymorphism, Lead and Sex. Biologic Research 2006 (in press).
65. Wilson SE, Kahn RS, Khoury J, Lanphear BP. Racial differences in cotinine among children exposed to environmental tobacco smoke. Chest 2006 (in press).
66. Wright J, Dietrich KN, Ris D, Wessel S, Lanphear BP, Hornung R. Childhood lead exposure and adult criminal behavior in a prospective, longitudinal cohort (submitted).

Editorials, Reviews and Commentaries

1. Lanphear BP. Hepatitis B immunoprophylaxis: Development of a cost effective program in the hospital setting. Infect Control Hospital Epidemiol 1990;11:47-50.
2. Lanphear BP. Trends and patterns in the transmission of bloodborne pathogens to health care workers. Epidemiologic Reviews 1994;16:437-450.

3. Kapil V, Lanphear BP. Tuberculosis - surveillance, prevention, and control. Occupational Environmental Medicine Report 1994;8:35-38.
4. Myers G, Davidson P, Weitzman M, Lanphear B. Contribution of heavy metals to developmental disabilities in children. Mental Retard Dev Dis 1997;3:239-245.
5. Lanphear BP. Transmission and control of bloodborne viral hepatitis in health care workers, in Occupational Medicine: State of the Art Reviews. McDiarmid MA, Kessler E, (eds), Hanley & Belfus, Inc. Philadelphia, PA, 1997;12:717-730.
6. Lanphear BP. Indoor Pollutants and Toxins, in *Ambulatory Pediatrics*, Green, Haggerty and Weitzman (eds.) 5th edition, 1999, W.B. Saunders Company, Philadelphia, PA.
7. Lanphear BP, Dietrich KN, Berger O. Prevention of lead toxicity in US children. Ambulatory Pediatrics 2003;3:27-36.
8. Sandel M, Phelan KJ, Wright R, Hynes HP, Lanphear BP. The effects of housing interventions on child health. Pediatr Ann 2004;33:474-481.
9. Breysse P, Farr N, Galke W, Morley R, Lanphear BP, Bergofsky L. The relationship between housing and health: children at risk. Environ Health Persp 2004;112:1583-1588.
10. Lanphear BP, Wright RO, Dietrich KN. Environmental toxins. Pediatrics in Review 2005;26:191-197.
11. Lanphear BP, Bearer CF. Biomarkers in paediatric research and clinical practice. Arch Dis Child. 2005;90:594-600.
12. Lanphear BP, Gergen PJ. Measuring Asthma Trends in US children (invited commentary). Am J Epidemiol 2003;158:105-107.
13. Lanphear BP. Origins and Evolution of Children's Environmental Health. Essays on the future of environmental health research: A tribute to Dr. Kenneth Olden. Environ Health Perspect 2005;24-32.
14. Lanphear BP, Vorhees CV, Bellinger DC. Protecting children from environmental toxins. PLoS Med. 2005;2(3):e61.
15. Lanphear BP. Lead Poisoning Prevention – Too Little, Too Late. JAMA 2005;293:2274-2276.
16. Wigle DT, Lanphear BP. Human Health risks from low-level environmental exposures: No apparent safety thresholds. PLoS Med 2005;2(12)e350.
17. Lanphear BP. Trials and tribulations of protecting children from environmental hazards. Environ Health Perspect 2006;114:1609-1612.

Letters

1. Menkhaus NA, Lanphear BP, Linnemann CC. Airborne transmission of varicella-zoster virus in hospitals. Lancet 1990;2:1315.
2. Lanphear BP. The resurgence of measles and herd immunity. JAMA 1992;268:789.
3. Lanphear BP, Linnemann CC, Cannon C. A high false positive rate of tuberculosis associated with Aplisol. J Infect Dis 1994;169:703-704.
4. Lanphear BP. Potential consequences of using Aplisol tuberculin tests in prior epidemic investigations. Infection Control Hospital Epidemiology 1995;16:255.

5. Canfield R, Henderson C, Lanphear BP. Intellectual impairment and blood lead levels. N Engl J Med. 2003;349:500-502.
6. Juskow T, Canfield RC, Henderson C, Lanphear BP. Comments on “Recent development in low level lead exposure and children’s intellectual abilities”. Environ Health Perspect 2005;113:A16.
7. Lanphear BP, Hornung R, Khoury J, Yolton K, Dietrich KN. Lead and IQ in Children. Environ Health Persp 2006;114:A86-A87.
8. Hornung R, Lanphear B, Dietrich K. Response to: "What is the meaning of non-linear dose-response relationships between blood lead concentration and IQ?" Neurotoxicology. 2006;27:635.

Presentations

1. “Biologic Hazards to Health Care Personnel in the Workplace”. University of Cincinnati, Cincinnati, Ohio, September 26, 1990.
2. “Common Misconceptions about Tuberculosis”. American Lung Association, St. Elizabeth’s Hospital, Belleville, IL, March 19, 1991.
3. “Prevention and Control of Infectious Disease in Health Care Workers”. Miami Valley Hospital, Dayton, OH, September 5, 1991.
4. “Hepatitis B Virus Infection in Health Care Workers”. Ohio University, Athens, Ohio, March 21, 1992.
5. “Universal Immunization Against Hepatitis B Virus”. Grand Rounds, Dayton Children’s Hospital, May 1992, Dayton, Ohio.
6. "Correlation of Blood Lead Levels and Dust Lead Levels Using Three Dust Collection Methods. Environmental Protection Agency, Research Triangle, N.C., January 20,1994.
7. "Relation of Lead-Contaminated House Dust and Blood Lead Levels in Urban Children" Environmental Protection Agency, Washington, D.C., February, 1994.
8. "Lead-Contaminated House Dust and Blood Lead Concentrations in Children", Society for Pediatric Research, Seattle, Washington May 5, 1994.
9. "EPA Health-Based Standards for Soil and Dust". Alliance to End Childhood Lead Poisoning, Washington, D.C., May 17, 1994.
10. "Epidemiology of Tuberculosis in Health Care Settings". University of Cincinnati, Cincinnati, OH, August 19, 1994.
11. "A Side-by-Side Comparison of Sampling Methods for Lead-Contaminated House Dust". American Public Health Association, Washington, D.C., November 1, 1994.
12. “Trends in Childhood Exposure to Lead: Implications for Prevention”. University of Rochester, Pediatric Grand Rounds, February 15, 1995.
13. “Childhood Exposure to Lead”. Visiting Professor, Nazareth College, Rochester, New York, March 24, 1995.
14. “Transmission and Control of Infections in Health Care Workers”. (Moderator & Speaker) American College of Occupational and Environmental Medicine, Las Vegas, Nevada, May 4, 1995.

15. "Lead Exposure Prevention Research at the University of Rochester". New England Lead Conference, Kennebunkport, Maine, August 3, 1995.
16. "Prevention of Childhood Lead Exposure". 1st Annual Midwest Conference on Childhood Lead Poisoning Prevention, Kansas City, MO, September 10-11, 1995.
17. "Childhood Lead Exposure: Implications for Occupational Health". National Institute for Occupational Safety and Health, Cincinnati, OH, May 10, 1996.
18. "Community Characteristics and Children's Blood Lead Concentrations". American Public Health Association, New York City, NY, November 19, 1996.
19. "Evolution of a Disease: The Science of Childhood Lead Exposure Prevention." American Public Health Association, New York City, NY, November 18, 1996.
20. "Childhood Lead Exposure: A Local and National Perspective." Occupational Medicine Grand Rounds, University of Rochester, January 2, 1997.
21. "Prevention of Childhood Lead Exposure: The U.S. Experience". (Keynote) University of the West Indies and Pan American Health Organization, Kingston, Jamaica, January 23, 1997
22. "Lead-Contaminated House Dust and Children's Blood Lead Levels". (Keynote Presentation) Look Out for Lead Conference, Madison, WI, May 22, 1997.
23. "Primary Prevention of Childhood Lead Exposure: A Randomized Trial of Dust Control". American Public Health Association, Indianapolis, November 13, 1997.
24. "Evolution of a Disease: Prevention of Childhood Lead Exposure." Pediatric Grand Rounds, Medical University of South Carolina, Charleston, SC, March 20, 1998.
25. "The Science of Childhood Lead Exposure Prevention." Tulane/Xavier Center for Bioenvironmental Research, New Orleans, May 4-5th, 1998.
26. "Lead Hazard Control Research" Conference on Linking Health, Housing & Environment, Centers for Disease Control, Department of Housing and Urban Development, National Institutes of Health, Phoenix, Arizona, June 21-24, 1998.
27. "A Randomized Trial of Dust Control to Prevent Childhood Lead Exposure." Presenter and Co-chairman, Section on Heavy Metals, 1st International Conference on Children's Environmental Health, Amsterdam, The Netherlands, August 11-13th, 1998.
28. "Prevention of Childhood Lead Exposure: A Critique of the EPA's Proposed Residential Lead Standard". Office of Children's Health Protection, U.S. Environmental Protection Agency, Washington, D.C., November 5, 1998.
29. "Science and Policy of Lead Poisoning Prevention in the United States". Nicholas School of the Environment, Duke University, Durham, North Carolina, February 22, 1999.
30. "Behaviors in Early Childhood and Exposure to Environmental Toxins". (invited) Pediatric Environmental Health Conference, San Francisco, CA May 4, 1999.
31. "Patterns of Lead Exposure in Early Childhood". International Conference on Lead Exposure, Reproductive Toxicity and Carcinogenicity, Gargnano, Italy, May 7, 1999.

32. "Adverse Effects of Blood Lead Concentrations <10 μg/dL" (Invited), 17th International Conference Neurotoxicology Conference, Little Rock, Arkansas, October 17-20, 1999.
33. "Emerging Research and Implications for Prevention of Childhood Lead Exposure" (Invited), 2nd Annual Syracuse Lead Conference, Syracuse, New York October 27th, 1999.
34. "Prevention of Lead Poisoning in Children" Sierra Club, Omaha, NE, November 16th, 1999.
35. "Children's Environmental Health: A Focus on Residential Hazards" Department of Pediatrics, University of Nebraska Hospital, November 17th, 1999.
36. "Effectiveness of Lead Hazard Controls", New England Lead Conference, New Hampshire, Tufts University School of Medicine, April 25, 2000.
37. "Subclinical Lead Toxicity in U.S. Children and Adolescents", Pediatric Academic Societies, Boston, MA, May 15, 2000.
38. "Contribution of Residential Exposures to Asthma in U.S. Children and Adolescents", Pediatric Academic Societies, Boston, MA, May 16, 2000.
39. "The Effect of Soil Abatement on Blood Lead Concentration in Children living near a former Smelter and Milling Operation" (invited). Coeur d'Alene, Idaho, May 24, 2000.
40. "The Paradox of Lead Poisoning Prevention" (invited). National Institute of Justice, Washington, D.C., July 18th, 2000.
41. "Evolution of a Disease: Prevention of Childhood Lead Exposure." Pediatric Grand Rounds, Children's Hospital Medical Center, Cincinnati, Ohio, August 22, 2000.
42. "Children's Environmental Health: A Focus on Residential Hazards" Pediatric Grand Rounds, Department of Pediatrics, University of Rochester School of Medicine, Rochester, NY, September 20th, 2000.
43. "Prevention of Lead Poisoning in Childhood" 7th Annual Childhood New York State Lead Poisoning Prevention Conference, Purchase College, NY, September 29, 2000.
44. "Excavating the Enigmas of Childhood Lead Exposure". Department of Environmental and Occupational Medicine, Harvard University School of Public Health, Boston, MA, October 16th, 2000.
45. "Contribution of Residential Exposures to Asthma". Eliminating Childhood Lead Poisoning: Our Challenge for the Decade, Centers for Disease Control and the U.S. Department of Housing & Urban Development, December 11th, 2000.
46. "Setting Research Priorities for the Decade". (Moderator & Speaker) Eliminating Childhood Lead Poisoning: Our Challenge for the Decade, Centers for Disease Control and the U.S. Department of Housing & Urban Development, December 13th, 2000.
47. "Evolution of a Disease: Prevention of Childhood Lead Exposure." (Keynote Presentation) Look Out for Lead Conference, Madison, WI, April 12, 2001.
48. "Environmental Lead Exposure and Children's Intelligence at Blood Lead Concentrations below 10 μg/dl." APA Presidential Plenary Session, Pediatric Academic Society Meeting, Baltimore, MD, April 30, 2001.
49. "Elimination of Childhood Lead Exposure: Obstacles & Opportunities" (Plenary). National Housing Conference and Exposition, New Orleans, LA, May 16th, 2001.

50. "Prevention of Childhood Lead Exposure: A Public Health Perspective" (Keynote Presentation). Philadelphia Health Department, Philadelphia, PA, May 23rd, 2001.
51. "Evolution of a Disease: Prevention of Childhood Lead Exposure." (Keynote Presentation), Charles Drew University, Los Angeles, California, October 22nd, 2001.
52. "Primary Prevention of Childhood Lead Exposure" (Keynote Presentation), Midwest Regional Lead Conference, Pittsburgh PA, October 29th, 2001.
53. "Prevention of Childhood Lead Exposure: Shifting to Primary Prevention" (Keynote Presentation), Indiana Department of Health, Lead-Safe Conference, November 7th, 2001.
54. "A Strategy for Primary Prevention of Childhood Lead Exposure" A testimony to Housing and Transportation Subcommittee, U.S. Senate, Washington, D.C., November 13, 2001.
55. "Ethical issues of Environmental Research involving Children" (moderator and speaker). Panelists were Jeffrey Kahn, Ph.D., and Leonard Glantz, J.D., Raleigh-Durham, North Carolina, NIEHS Conference of Children's Environmental Health Centers, January 23, 2001.
56. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." Grand Rounds, Omaha Children's Hospital, Omaha, Nebraska, March 1, 2002.
57. "Racial Disparities in Children due to Environmental Hazards" Ohio Commission on Minority Health, Columbus, Ohio March 27, 2002.
58. "Prevention of Childhood Lead Exposure in a Former Mining Community" Tar Creek, Oklahoma, April 4, 2002.
59. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." Grand Rounds, Hasbro Children's Hospital, Brown University, Providence Rhode Island, May 17, 2002.
60. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." Grand Rounds, Dayton Children's Hospital, Wright University, Dayton, Ohio May 22, 2002.
61. "Evolution of a Disease: Science and Prevention of Childhood Lead Exposure." International Lead Congress, Washington, DC, June 3rd, 2002.
62. "Residential Hazards: A Neglected Health Problem" Agency for Toxic Substances Disease Registry, Centers for Disease Control and Prevention, Atlanta, Georgia, August 19th, 2002.
63. "Control of Residential Exposures to Environmental Neurotoxins" National Center for Healthy Homes (Moderator and Speaker), Annapolis, VA, November 7th, 2003.
64. "The Promises and Potential Pitfalls of Primary Lead Poisoning Prevention" Purchase College, 9th Annual Childhood New York State Lead Poisoning Prevention Conference, Purchase College, New York,, October 4th, 2002.
65. "Evolution of a Disease: the Science and Prevention of Childhood Lead Exposure." Pediatric Grand Rounds, Syracuse, NY, October 9th, 2002.
66. "Evolution of a Disease: the Science and Prevention of Childhood Lead Exposure."
67. University of Texas at El Paso, El Paso, Texas January 29th, 2003.
68. "Childhood Lead Poisoning" Introduction to Children's Environmental Health, Seattle, Washington, Pediatric Academic Society, May 3rd, 2003.

69. "The Legacy of Lead: Childhood Lead Poisoning in the 21st Century". Chicago Lead Summit, Chicago, Illinois, May 28th, 2003.
70. "The Legacy of Lead: Childhood Lead Poisoning in the 21st Century". Case Western Reserve University, Cleveland, Ohio, June 3rd, 2003.
71. "Housing and Children's Health", Sprawl: The impact on vulnerable populations, University of Cincinnati College of Medicine, Cincinnati, Ohio, July 8th, 2003.
72. "Trials and Tribulations of Protecting Children from Environmental Toxins". Duke University, Nicholas School of the Environment, Durham, NC, November 6th, 2003.
73. "Adverse Effects of Fetal and Childhood Exposures to Prevalent Toxins" Midwest Critical Regional Neonatology Conference, Covington, KY, November 14th, 2003.
74. "Control of Residential Hazards in Children" American Public Health Association, San Francisco, CA, November 18th, 2003.
75. "Low-Level Exposure to Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis". 21st International Neurotoxicology Conference, Honolulu, Hawaii, February 11th, 2004.
76. "Trials and Tribulations of Protecting Children from Environmental Hazards" Workshop on Ethical Issues on Children's Environmental Health, Children's Environmental Health Network, Washington, D.C. March 5, 2004.
77. "Low-Level Exposure to Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis", Pediatric Academic Societies Annual Meeting. Pediatric Research 2004;55:163A.
78. "The Impact of the Environment on Children's Health" Bob Smith Endowed Lecture, Department of Pediatrics, First Gulf Coast Children's Environmental Health Symposium, Baylor University, Houston, Texas.
79. "The Search for Environmental Causes of Learning Disabilities, Learning Disabilities Initiative, Baltimore, MD, May 18th, 2004.
80. "Residential Hazards in Children: A Neglected Public Health Problem", Pediatric Grand Rounds, Boston Medical Center, Boston University Medical Center, Boston, MA, May 20th, 2004.
81. "Residential Hazards in Children" "Healthier Homes, Stronger Families: Public Policy Approaches to Healthy Housing", National Center for Healthy Housing, Washington, D.C., June 2nd, 2004.
82. "Fetal and Early Childhood Exposures to Prevalent Toxins" Pediatric Grand Rounds, Ste. Justine Children's Hospital, University of Montréal, Montreal, Canada, June 16th, 2004.
83. "Childhood Exposure to Lead-Contaminated Soil: A Problem of the Past or a Problem from the Past?" National Academy of Science Committee on Superfund Site Assessment and Remediation in Coeur d'Alene River Basin", June 17th, 2004, Coeur d'Alene, Idaho.
84. "The Legacy of Lead" (Keynote Speaker). Chicago Lead Summit, Region V EPA Headquarters, September 15th, 2004.
85. "A Tale of Two Toxins: Children's Exposure to Tobacco and Lead" (with Michael Weitzman), The American Academy of Pediatrics, San Francisco, CA, October 10th, 2004.

86. "A Legacy of Childhood Lead Poisoning" University of Washington, Seattle, Washington, October 30, 2004.
87. "Protecting Children from Environmental Toxins", Pediatric Grand Rounds, Seattle Children's Hospital, Seattle Washington, March 10th, 2005.
88. "The Science and Politics of Childhood Lead Poisoning", Northwest Pediatric Environmental Health Conference, University of Washington, Seattle, Washington, March 11th, 2005.
89. "The Effects of Low-level Exposure to Environmental Toxins during Fetal Development and Early Childhood", Children's' Hospital of Fudan University, Shanghai International Pediatric Forum, Shanghai, China, June 16th to 18th, 2005.
90. "The Role of Biomarkers in Revealing Genetic and Environmental Influences of Disease and Disability" Psychiatry Grand Rounds, University of Cincinnati, February 8th, 2006.
91. "Trials and Tribulations of Protecting Children from Environmental Hazards: Ethical Issues", Johns Hopkins University of Medicine, March 17th, 2006.
92. "Key Elements of a Primary Prevention Strategy for Lead Poisoning", Albany Law School, Union University, Albany, New York, March 16th, 2006.
93. "Low-Level Lead Toxicity: The Ongoing Search for a Threshold"", Case Western Reserve University, City Club of Cleveland, Cleveland, OH March 4th, 2006.
94. Integrating Genetic and Environmental Influences in Pediatric Research" (Moderator and Speaker), Pediatric Academic Societies, San Francisco, CA, April 30th 2006.
95. "Ethical Issues in Housing Health Hazard Research Involving Children" (Topic Symposia) Pediatric Academic Societies, San Francisco, CA, May 2nd 2006.
96. "Low-Level Lead Toxicity: The Ongoing Search for a Threshold"", International Workshop on Neurotoxic metals: from Research to Prevention, University of Brescia, Italy, June 17th, 2006.
97. "Efficacy of HEPA-CPZ Air Cleaners on Unscheduled Asthma Visits and Asthma Symptoms", International Society for Environmental Epidemiology, Paris France, September 6th, 2006.
98. "Protecting Children from Environmental Toxins", Region VIII Children's Environmental Health Summit, Vail, Colorado September 20th, 2006,.
99. "Integrating Genetic and Environmental Biomarkers in Pediatric Epidemiology", Visiting Professor, Simon Fraser University and University of British Columbia, Vancouver, British Columbia, October 19th-20th, 2006.
100. "The Legacy of Lead", Indiana Lead Conference, Indianapolis, Indiana, October 24, 2006.
101. "Ethical dilemmas in Children's Environmental Health", Seminar Series in Ethics of Toxicology, University of Champagne-Urbana, Champagne, Illinois, November 19th, 2006.
102. "Low-Level Lead Toxicity: Implications for Prevention"", WHO Informal Workshop on Lead, University of Munich, Germany, November 30th, 2006.
103. "Low-Level Lead Toxicity: The Ongoing Search for a Threshold"", National Environmental Public Health Conference, National Centers for Disease Control, Atlanta, Georgia, December 4th, 2006.
104. "The Epidemiologic Conquest of Childhood Lead Toxicity: A Pyrrhic Victory". NIEHS Workshop on Children's Environmental Health Research: Past, Present and Future. January 22nd, 2007.
105. "Efficacy of HEPA-CPZ Air Cleaners on Unscheduled Asthma Visits and Asthma Symptoms", Pediatric Academic Societies, APA Presidential Platform Plenary Session, Toronto, Canada, May 7th, 2007.

106. “Linking Low-level Exposures to Environmental Toxicants with ADHD”. Duke Integrated Toxicology and Environmental Health Program Symposium on Developmental Neurobehavioral Disabilities and Toxic Exposures, March 23, 2007, Durham, North Carolina.

Grants

1. Principal Investigator, "Dust-Lead and Blood Lead Levels among Urban Children". The National Center for Lead-Safe Housing, $561,619, 06/15/93 to 08/31/94. Department of Housing and Urban Development Contract MDLPT0001-93. (25% effort).
2. Principal Investigator, "Determinants of Lead Exposure among Children in Monroe County, NY", NIEHS Pilot Grant, University of Rochester School of
3. Principal Investigator, "The Effectiveness of Dust Control in Reducing Children's Blood Lead Levels" U.S. Department of Housing and Urban Development, $128,394, 04/01/94 to 05/30/95. (25% effort).
4. Principal Investigator, "Primary Prevention of Exposure to Lead". Centers for Disease Control and Prevention, $832,228, 09/30/94 to 10/01/98. (25% effort)
5. Principal Investigator, "Lead-Contaminated House Dust and Children's Blood Lead Levels". National Center for Lead-Safe Housing, $43,260, 10/01/96 to 03/30/96. (25% effort).
6. Co-investigator (Christy, PI), “Tuberculosis Screening in Children”. New York Department of Health, $15,000, 01/01/95 to 12/31/96. (0% effort)
7. Co-investigator (Weitzman, PI), “Fellowship Training in General Pediatrics” (Grant # D28PE50008). Bureau of Health Professions, HRSA, U.S. Public Health Service, $1,752,816, 06/01/96 to 05/30/97. (10% effort).
8. Principal Investigator, “Neurobehavioral Effects of Low-Level Lead Exposure in Children”. University of Rochester School of Medicine and Dentistry, $8,560, 06/01/96 to 05/30/97. (0% effort)
9. Principal Investigator, “Neurobehavioral Effects of low-level Lead Exposure in Children”. NIEHS Pilot Grant, University of Rochester Department of Environmental Medicine, $20,035, 09/01/97 to 08/30/97. (0% effort).
10. Co-investigator (Howard, PI), “Effect on Breastfeeding of Pacifiers and Bottle Feeding”. Bureau of Maternal and Child Health, $420,333, 10/01/96 to 09/30/00. (2.5% effort)
11. Co-investigator (Canfield, PI) “Lead and Children’s Cognitive Functioning”, Research Grants Program, Cornell University. $17,000, 10/01/96 to 09/31/97 (0% effort).
12. Principal Investigator, “Neurobehavioral Effects of Low-Level Lead Exposure in Children” (RO1-ES 08338). National Institute of Environmental Health Sciences, 12/01/96 to 11/31/01, $1,946,848. (25% effort).
13. Co-investigator, (Aligne, PI) “Reduction in Passive Smoking among Children with Asthma: A Randomized Trial of HEPA Air Filtration”. 10/01/96 to 09/31/97, $6,000. KIDD Grant, Rochester General Hospital (0% effort).
14. Co-investigator, (DeWitt, PI). “Faculty Development in General Pediatrics”. Bureau of Health Professions, Health, Department of Health and Human Services 07/01/97 to 06/30/00, $338,000. (15% effort).
15. Principal Investigator, “A Side-by-Side Comparison of Allergen Sampling Methods”, U.S. Department of Housing and Urban Development, 01/02/98 to 12/31/98, $163,065. (15% effort).

16. Principal Investigator, “National Research Service Award - Fellowship Training in General Pediatrics and Adolescent Medicine” (1T32PE10027), Health Resources and Services Administration, DHHS. 07/01/98 to 06/30/03. $634,408. (0% effort).
17. Co-investigator, (Steiner, PI) “Survey of Directors and Graduates of NRSA Fellowship Training Programs”, Health Resources and Services Administration, Department of Health and Human Services. 06/01/98 to 06/30/99.
18. Principal Investigator, “Effect of Soil Remediation on Children’s Blood Lead Levels in Midvale, Utah: An Observational Study”. U.S. Environmental Protection Agency, 08/01/98 to 07/30/99. $62,550. (15% effort).
19. Co-investigator, (Phelan, PI) Trends and Patterns in Playground Injuries among U.S. Children.” Ambulatory Pediatric Association, 05/05/99 to 05/04/00. $9,000 (0% effort).
20. Principal Investigator, “Risk Assessment for Residential Lead Hazards”. U.S. Department of Housing and Urban Development, 09/01/99 to 08/30/00. $102,435. (25% effort).
21. Principal Investigator, “Residential Exposures associated with Asthma in U.S. Children and Adolescents” U.S. Department of Housing and Urban Development, 07/16/99 to 03/15/00. $30,400. (20% effort).
22. Principal Investigator, “Effectiveness of Lead Hazard Control Interventions – A Systematic Review" National Center for Lead-Safe Housing, 10/01/99 to 06/01/00. $22,500 (10% effort).
23. Principal Investigator, “Racial Disparity in Blood Lead Levels due to Genetic Variation in Calcium Absorption”. NIEHS Pilot Grant, Center for Environmental Genetics, University of Cincinnati, 04/01/00 to 03/31/01. $28,130 (0% effort).
24. Principal Investigator, “International Pooled Analysis of Prospective, Lead-Exposed Cohorts”. National Institute of Environmental Health Sciences, National Institutes of Health, 08/15/00 to 09/14/01, $16,000. (2.5% effort).
25. Principal Investigator, “A Randomized Trial to Reduce ETS in Children with Asthma” (RO1-HL/ES65731). National Heart, Lung and Blood Institute, National Institutes of Health, 09/29/00 to 09/28/04, $1,546,848. (25% effort).
26. Co-investigator, (Geraghty, PI) “Breastfeeding Practices of Mothers of Multiples”. Ambulatory Pediatric Association, 05/01/01 to 04/30/02. $5,000 (0% effort).
27. Principal Investigator (Subcontract), “A Longitudinal Study of Lead Exposure and Dental Caries”. National Institute of Dental and Craniofacial Research, National Institutes of Health, 08/01/01 to 07/30/04. $300,000 (10% effort).
28. Co-investigator (Phelan, PI), “Fatal and Non-Fatal Residential Injuries in U.S. Children and Adolescents” U.S. Department of Housing and Urban Development, 03/01/01 to 11/31/01. $40,700. (5% effort).
29. Principal Investigator, “Prevalent Neurotoxicants in Children” (PO1-ES11261). National Institute for Environmental Health Sciences and U.S. Environmental Protection Agency, 09/01/01 to 09/31/06, $5,000,000. (30% effort).
30. Principal Investigator, “International Pooled Analysis of Lead-Exposed Cohorts”. Centers for Disease Control (RO1/CCR 521049). Centers for Disease Control, 09/15/01 to 09/14/02, $28,473. (3% effort).

31. Principal Investigator, supplement to “Prevalent Neurotoxicants in Children” (PO1-ES11261). NIEHS, 09/01/02 to 09/31/07, $1,800,000. (10% effort).
32. Co-Investigator, “ADHD Phenotype Network: Animal Model to Clinical Trial”. National Institute of Neurologic Diseases, 09/15/02 to 06/30/05 (15% effort).
33. Principal Investigator, “National Research Service Award - Fellowship Training in Primary Care Research (1T32PE10027), Health Resources and Services Administration, DHHS. 07/01/03 to 06/30/09. $1,600,000. (0% effort).
34. Principal Investigator, “Linkage of ADHD and Lead Exposure”, Springfield, Ohio Department of Health, 02/01/03 to 06/01/04, $25,000. (0% effort).
35. Co-investigator (Yolton, PI) “Explorations of ETS Exposure on Child Behavior and Sleep” NIEHS, 04/01/04 to 03/30/06, $300,000. (5% effort).
36. Co-Investigator and Mentor (Kahn, PI). “Childhood Asthma in an Era of Genomics: Will the Generalist’s Role be Recast?“ Robert Wood Johnson Generalist Physician Faculty Scholars Program” 06/01/04 to 05/30/08, $300,000.
37. Co-investigator (Haynes, PI) “MRI as a Biomarker of Manganese Exposure”. NIEHS, 09/01/04 to 08/30/06, $300,000. (5% effort).
38. Co-investigator and Mentor (Phelan, PI) “Childhood Residential Injury and Caregiver Supervision”, National Institute for Child Health and Development, 06/01/05 to 05/30/10, $600,000. (0% effort).
39. Co-investigator (National Center for Healthy Housing, PI) “Development of a Standardized Housing Assessment for Asthma”, U.S. Department of Housing and Urban Development, 11/01/05 to10/31/07, $50,000. (5% effort).
40. Co-investigator (Sub-Contract PI), BYPL Vanguard Center (Specker, Principal Investigator), “National Children’s Study”, National Institute for Child Health and Development, 11/01/05 to 10/31/10, $500,000. (20% effort).
41. Co-Investigator and Mentor (Wilson, PI), “Racial Difference in DNA Adducts in Tobacco-Exposed Children”. Dean’s Scholar Award, University of Cincinnati, 02/22/06 to 01/21/09, $150,000 (5% effort).
42. Co-Investigator and Mentor (Geraghty, PI) “Role of Environmental Chemicals on Lactation Outcomes (1 K23 ES014691-01). National Institute for Environmental Health Sciences, 06/01/06 to 05/30/11, $600,000. (0% effort).
43. Co-Investigator and Mentor (Spanier, PI), “Exhaled Nitric Oxide to Manage Childhood Asthma”. National Heart, Lung and Blood Institute, 07/01/06 to 06/31/08, $200,000 (10% effort).
44. Co-Investigator (Hershey, PI) “Epithelial Genes in Allergic Inflammation” National Institutes of Allergy and Infectious Diseases”, 07/01/06 to 06/30/11, $4,787.541. (3% effort).
45. Co-Investigator (Spanier, PI). “Low Level Prenatal Tobacco Exposure and Infant Wheeze”. Young Clinical Scientist Award, Flight Attendant Medical Research Institute”, 07/01/07 to 06/30/10, $300,000. (5% effort).
46. Co-Investigator (Yolton, PI). “Tobacco Smoke and Early Human Behavior”. Clinical Innovator Award, Flight Attendant Medical Research Institute”, 07/01/07 to 06/30/10, $300,000. (3% effort).
47. Principal Investigator, “A Randomized Trial to Prevent Childhood Lead Poisoning and Residential Injuries”, National Institute for Environmental Health Sciences, 03/01/07 to 02/28/12, $2,500,000. (25% effort).