Do Environmental Exposures Cause ADHD?

- David O. Carpenter, M.D.
- Institute for Health and the Environment
- University at Albany
- Rensselaer, NY
Childhood Hyperkinesis, or Attention-Deficit Hyperactivity Disorder (ADHD), is a behavior disorder characterized by three main, partly interrelated, symptoms: inattentiveness, overactivity, and impulsiveness.

The ADHD child shows inattentiveness by attending to each stimulus for only a brief period before changing the focus of attention to something else.

Two-thirds of ADHD children show comorbidity with another psychiatric illness, such as autism, dyslexia, conduct disorder or oppositional defiant disorder as well as learning disability.
Genetic and Other Risk Factors

- Twin and adoption studies show a genetic component. Monozygotic twins show 50% or more concordance while dizygotic twins show up to 33% concordance. Specific genes have not been identified.
- There are reports of a 2 to 8-fold elevated risk that a child of a parent with ADHD will develop ADHD.
- These facts indicate a contribution of inherited and environmental factors, and suggest that epigenetic changes and gene-environment interactions are critical.
Risk Factors for ADHD

- Being male (OR = 3.05, 95% CI = 2.30-3.98).
- Poor maternal diet.
- Maternal stress.
- Prenatal or early-life exposure to environmental chemicals.
- High maternal and paternal education are protective (OR = 0.57, 95% CI = 0.42-0.78).
Attention Deficit/Hyperactivity Disorder

- One peculiar aspect of the disorder is that it affects more boys than girls. The behavioral problems of ADHD boys seem to differ from those of ADHD girls. The primary deficit in girls usually is attention problems without hyperactivity (Predominantly Inattentive Type) while the primary deficit in the boys usually is overactivity and impulsiveness (Predominantly Hyperactive-Impulsive Type).
- Brain volume is about 5% smaller in ADHD children as compared to controls.
Cognition in ADHD

- ADHD is not usually associated with large reductions in intelligence, but children with ADHD do poorly on IQ tests.
- The major deficit in ADHD is working memory, the ability to hold something in mind while doing something else or to use information to perform an action.
- Cognitive flexibility, the ability to switch attention from one thing to another, is very reduced in ADHD children.
- It is difficult to learn if you can’t pay attention!
Figure 1.
Cumulative Frequency Distribution of Verbal IQ Scores in Subjects with Low or High Levels of Lead (n=158)

Figure 3.

Teachers' Ratings and Dentin Lead Levels (n=2146)

# Effects of Lead on Cognitive and Behavioral Traits

<table>
<thead>
<tr>
<th>ADHD</th>
<th>LD</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ hyperactivity</td>
<td>↓ reading, math</td>
<td>↓ fine motor</td>
</tr>
<tr>
<td>↑ impulsivity</td>
<td>↓ spelling</td>
<td>↓ visual motor</td>
</tr>
<tr>
<td>↑ distractibility</td>
<td>↓ pattern recognition</td>
<td>↑ aggressive</td>
</tr>
<tr>
<td>↑ dif. w. instructs</td>
<td>↓ word recognition</td>
<td>↑ antisocial</td>
</tr>
<tr>
<td>↑ conduct problems</td>
<td></td>
<td>↑ off-task</td>
</tr>
<tr>
<td>↓ executive function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ attention/vigilance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ social skills</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. AOR for ADHD among U.S. children, NHANES 1999–2002, by blood lead concentration (μg/dL). The model was adjusted for child’s age, sex, race/ethnicity, preschool attendance, serum ferritin, prenatal ETS exposure, smoker in the household, and insurance status. 

*p-value for trend = 0.012.*
**Figure 2.** Dose–response relationship between blood lead and behavior. Smooth functional term relating behavior Z-scores to blood lead in an adjusted generalized additive mixed model, adjusting for age, sex, hemoglobin, average monthly income, maternal and paternal education, and number of other children and accounting for clustering at school and classroom level. Social problems were not significantly nonlinear (effective degrees of freedom = 1.56).

Fig. 3. Regression of fitted MDI_36 score on log-transformed concentrations of cord blood lead level grouped by gender.
Figure 1. Dose–response functions for PCB–IQ effect expressed in true exposure intervals: Full Scale IQ (A), Verbal IQ (B), Freedom from Distractibility (C), and Verbal Comprehension Index (D). Adjusted means ± SE are plotted against the median PCB concentration within each interval, nondetectable to 0.99, 1.00–1.49, 1.50–1.99, 2.00–2.49, and ≥ 2.50 ppb. Linear F-tests (Braver and Sheets 1993) showed significant linear dose–response relationships between PCB concentrations and Full Scale IQ, Verbal IQ, and Freedom from Distractibility (all $p < 0.05$).
Neurotoxic Effects of Developmental PCB Exposure

- Decreased IQ
- Impulsivity
- Attention problems
- Poor school performance/language processing
- Deficient social behavior
- Blurring of gender-specific behavior
**Table 6.** Comparison of cognitive domains affected in ADHD and by lead and PCBs in humans and laboratory species: degree of confidence in findings.

<table>
<thead>
<tr>
<th>Domain</th>
<th>ADHD</th>
<th>Lead Human</th>
<th>Lead Animal</th>
<th>PCBs Human</th>
<th>PCBs Animal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>—</td>
<td>++</td>
</tr>
<tr>
<td>Nonverbal (incl. spatial)</td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td>—</td>
<td>++</td>
</tr>
<tr>
<td>Response inhibition</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Planning</td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vigilance (sustained)</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Alertness</td>
<td>++</td>
<td>+++</td>
<td></td>
<td></td>
<td>++</td>
</tr>
</tbody>
</table>

Pluses indicate range of degree of confidence, from low (+) to high (+++). — indicates that literature does not support involvement of the domain.

Eubig PA, Aguiar A, Schantz SL. Lead and PCBs as risk factors for attention deficit/hyperactivity disorder. Environ Health Perspect. 2010 Dec;118(12):1654-67
Mean +/- SE WISC-IV score per quintile of prenatal urinary DAP concentration Full-Scale IQ


**Figure 1.** Log-linear regression line for reading scores by serum cotinine levels. Dashed lines indicate 95% confidence interval.

**Figure 2.** Log-linear model for cotinine (solid line) versus linear models for cotinine among children with cotinine above and below 1 ng/mL (dashed lines; ~ 80th percentile).
Figure 2. AOR for ADHD among U.S. children by prenatal ETS exposure and sex. The risk for ADHD among ETS-exposed children was greater in females; females who were prenatally exposed to tobacco were at 4.6-fold higher risk for ADHD compared with unexposed females (OR = 4.6; 95% CI, 1.7–12.4), whereas exposed males were at 2-fold higher risk for ADHD compared with unexposed males (OR = 2.1; 95% CI, 0.9–4.7) (p = 0.141 for sex by prenatal ETS exposure interaction). Model adjusted for race/ethnicity, sex, age, blood lead level, ferritin level, presence of a smoker in the home, preschool attendance, and insurance status.

Fig. 1. Percentage of subjects with behavioral problems (mild and severe problems combined) by exposure group.
Mercury
Effects of Low Dose Prenatal Exposure

Figure shows prenatal mercury exposure levels of Faroese children with scores in the lowest quartile after adjustment for cofounders. For each of the five major cognitive functions, one neuropsychological test with a high psychometric validity was selected.


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Fig. 1  Proportion of children with different blood mercury levels.
<table>
<thead>
<tr>
<th></th>
<th>Parental report of ADHD</th>
<th>With prescription medication use (adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
<td>Adjusted(^a)</td>
</tr>
<tr>
<td>PFOS</td>
<td>1.03 (1.01–1.05)</td>
<td>1.03 (1.01–1.05)</td>
</tr>
<tr>
<td>PFOA</td>
<td>1.17 (1.07–1.30)</td>
<td>1.12 (1.01–1.23)</td>
</tr>
<tr>
<td>PFHxS</td>
<td>1.07 (1.01–1.12)</td>
<td>1.06 (1.02–1.11)</td>
</tr>
<tr>
<td>PFNA</td>
<td>1.76 (1.39–2.23)</td>
<td>1.32 (0.86–2.02)</td>
</tr>
</tbody>
</table>

\(^a\)Adjusted for NHANES sample cycle, age, sex, race, ETS, and maternal smoking during pregnancy.


<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Total sample (n)</th>
<th>Cases (n)</th>
<th>Crude odd ratios</th>
<th>Adjusted odd ratios*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4,5-TCP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below the LOD</td>
<td>1776</td>
<td>145</td>
<td>Referent group</td>
<td>Referent group</td>
</tr>
<tr>
<td>&lt;Median (1.03 μg/g)</td>
<td>367</td>
<td>30</td>
<td>1.27 (0.78 to 2.06)</td>
<td>1.01 (0.47 to 2.20)</td>
</tr>
<tr>
<td>≥Median (1.03 μg/g)</td>
<td>368</td>
<td>24</td>
<td>0.89 (0.48 to 1.65)</td>
<td>0.98 (0.48 to 1.99)</td>
</tr>
<tr>
<td>p for trend</td>
<td>—</td>
<td>—</td>
<td>0.72</td>
<td>0.95</td>
</tr>
<tr>
<td>2,4,6-TCP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below the LOD</td>
<td>846</td>
<td>56</td>
<td>Referent group</td>
<td>Referent group</td>
</tr>
<tr>
<td>&lt;Median (3.58 μg/g)</td>
<td>834</td>
<td>84</td>
<td>1.84 (1.25 to 2.72)</td>
<td>1.54 (0.97 to 2.43)</td>
</tr>
<tr>
<td>≥Median (3.58 μg/g)</td>
<td>834</td>
<td>59</td>
<td>1.56 (1.12 to 2.16)</td>
<td>1.77 (1.18 to 2.66)</td>
</tr>
<tr>
<td>p for trend</td>
<td>—</td>
<td>—</td>
<td>0.008</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, poverty-to-income ratio, maternal smoking during pregnancy, low birth weight, blood lead and serum cotinine.
LOD, limit of detection; TCP, trichlorophenol.
What are the Long-Term Consequences of Exposure to these Contaminants?

- Of children with ADHD, about half will show symptoms as adults.
- There is increasing evidence that the reduced ability to deal with frustration increases the risk of anti-social behavior throughout life.
- The evidence for this is strongest for lead exposure, but probably applies to the other substances that show this profile of reduced IQ and behavioral changes.
Does Early-life Exposure to Environmental Chemicals Increase Risk of Crime?

- Wright et al. (2008) found that an elevated child’s blood lead level at 6 years of age significantly increased risk of arrest for violent crime as a young adult (OR-1.5; 95%CI = 1.1-1.9).

- Nevin (2000) compared historic use of lead in gasoline to arrests for violent crime 20 years later and found significant correlation.
20th Century Trends in Lead Exposure and USA Murder Rate

- 1900-1960 murder rate tracked rise and fall of lead paint, with 21-year lag
- 1960-2000 murder tracked rise and fall of leaded gas, with 18 year lag
- Gas lead settled over weeks/months, circa-1900 paint chalked after 3 years
- Murder rate peaked near 10 per 100,000 about two decades after:
  - Early-1900s paint lead peak
  - 1956 interim gas lead peak
  - Early-1970s gas lead peak
  - Early-1960s peak additive exposure (air and paint lead) in city slums
Shifts in Age-Specific Incarceration Rates

- Incarceration rates fell from 2000-2006 for males under 30, due to fall in preschool blood lead since mid-1970s.
- Over-age-40 incarceration rising - born when lead poisoning epidemic
- Age 30-39 male incarceration rose slightly from 2000-2006, but rate for black males fell 12%, reflecting birth years over 1960s when blacks were disproportionately displaced by slum clearance
Figure 1. Model showing how distinct neurobiological pathways might lead to overlapping but separable cognitive profiles and similar behavioral patterns. ADHD, attention-deficit/hyperactivity disorder.

The Relationship Between IQ and Neurobehavior

- In a meta-analysis Marcus et al. (2010) concluded that concentrations of lead that result in decrements of IQ are the same concentrations that result in shortened attention span and anti-social behavior.

- While there are fewer studies with other contaminants that reduce IQ, it is likely that the same relation applies for PCBs, methyl mercury, ETS, pesticides, PFCs, phthalates and possibly many other contaminants.
The Developing Brain

- For almost all of the chemicals associated with ADHD there is strong evidence that prenatal exposure is more harmful than post-natal exposure.
- We must find ways of reducing exposure of pregnant women to these toxicants.
- Unfortunately some of these chemicals are persistent compounds, and we cannot wait until a woman is pregnant to take steps to reduce levels of these substances in air, food, water and consumer products.
Conclusions

- ADHD is a serious disease that is increasing in incidence as well as diagnosis.
- While there is a clear genetic component, the discordance even in monozygotic twins indicates gene-environment interactions.
- While the neuronal pathways which relate intelligence to neurobehavior are poorly understood, those environmental chemicals that cause a reduced IQ also cause shortened attention, hyperactivity and anti-social behavior.
- ADHD is best understood to be a disease that results from exposure to a number of different neurotoxic environmental contaminants in genetically susceptible individuals.