A Developmental Perspective on Lead Neurotoxicity

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Key Elements of a Developmental Perspective

- Early stages of development shape and constrain the ways in which later development unfolds
- Developmental domains are not independent of one another
- The relationship between child and environment one of reciprocal influence; child an active agent in creating the developmental context

Why does it matter?

- A developmental perspective provides a framework of assumptions and concepts that can:
-
  - Organize existing data
  - Suggest potential causal factors and pathways
  - Identify fruitful avenues for treatment and future research

One Example

- Lead-associated deficits often characterized as permanent, but what is this based on?
- “Persistent” is not same as “permanent”
- Few studies look at the natural history of a deficit, specifically factors that influence its developmental trajectory
- Prevents consideration of interventions that might improve the prognosis

Principle 1

The nature, severity, and persistence of the effects of early-life exposure to lead depend on contextual factors

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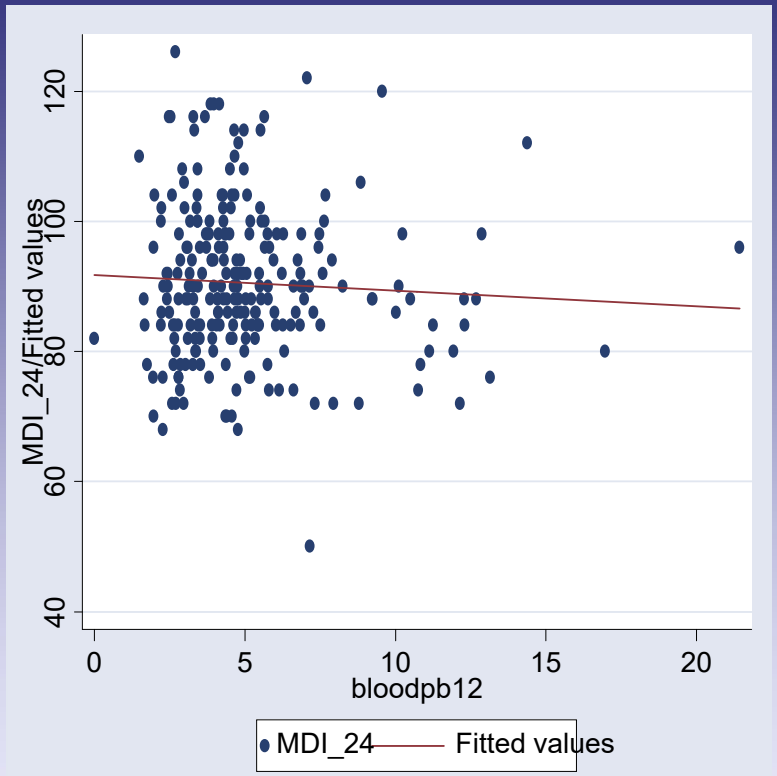
- Acknowledged that impact of a neurotoxicant varies with developmental stage (critical windows of vulnerability)
- Some attention to effect modification by chemical co-exposures (mixtures), less to biological, nutritional, psychological factors
- Increasing recognition of the need for a broad view of what contributes to “exposome”

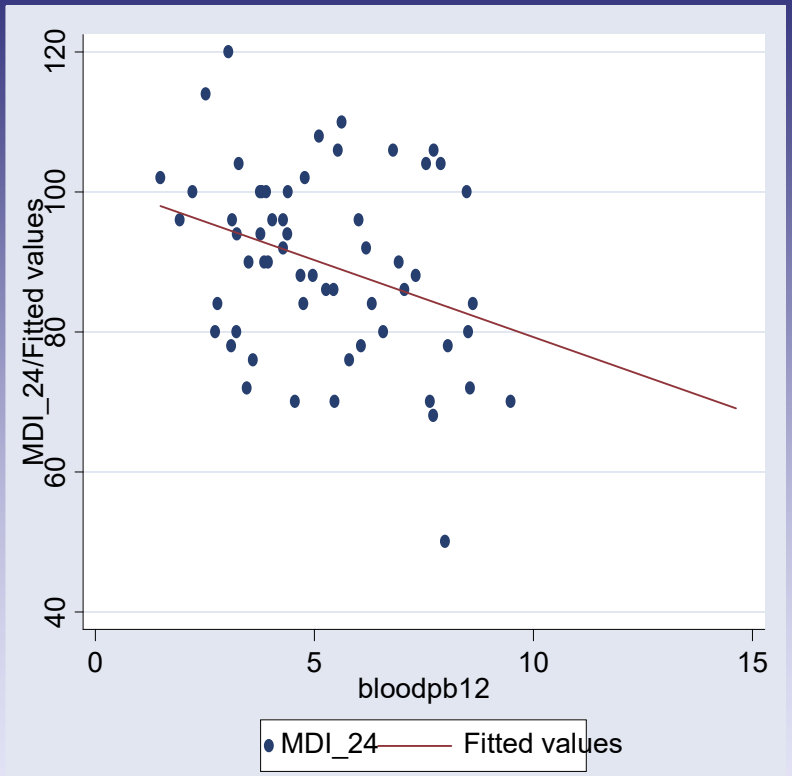
1. Impact of Lead Exposure When a Component of a Mixture (Mn)

Plots of MDI scores vs Blood Lead by Quintiles of Blood Mn

Lowest 4 Quintiles of Blood Mn



Highest Quintile of Blood Mn



Claus Henn et al., *Environ Health Perspect* 2012;120:126-131

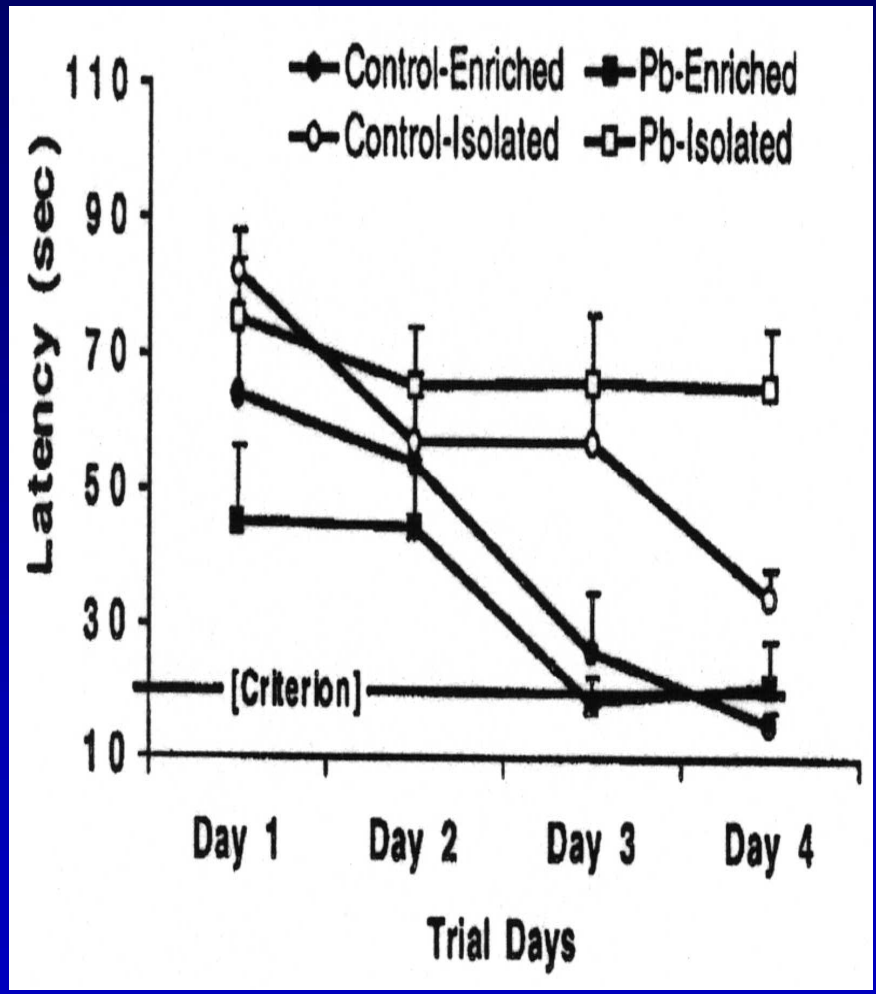
Physical and Psychosocial Context as a Modifier of Lead's Impact

- Observational studies: severity of deficit and persistence greater for children of lower SES or in environments less developmentally supportive:
  - PAHs (Vishevetsky et al., 2015)
  - $PM_{2.5}$ (Morelli et al., 2016)

- Quantile regression of inverse association between blood lead and end-of-grade achievement test scores showed impact disproportionately greater on children at low end of performance distribution, i.e. those already at increased risk for scoring poorly (Magzamen et al., 2015)

Reversal of a Lead-Associated Neurobehavioral Deficit by Environmental Enrichment

- rats lead-exposed during gestation and lactation
- spatial learning assessed with a water maze (50 days of age)
- performance of lead-exposed enriched rats = enriched controls and > isolated controls
- in lead-exposed enriched rats, induction of BDNF mRNA expression in hippocampus and recovery of deficits in gene expression of NR1 subunit of NMDAR in hippocampus (CA1-CA4) and granule cell layer of dentate gyrus



Guilarte et al., *Ann Neurol* 2003;53:50-56

Environmental Enrichment Interventions

- Improve cognitive skills of children with other challenges:
  - low birth weight
  - ADHD
  - epilepsy
- Increase cognitive/emotional stimulation provided by parents, parent-child communication, reduce stress
  - protein-calorie malnutrition
  - iron deficiency anemia
  - maternal smoking

Principle 2

Deficits caused by early-life exposure to lead initiate processes that can result in pathologies that differ from those observed initially (and might not even be clearly associated with the exposure)

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Deficits caused by early-life exposure initiate developmental processes that can result in pathologies that differ from those observed initially (and might not even be clearly associated with the exposure)

- **Inter-dependence of developmental domains**
- **Developmental cascades**
- **Silent or delayed neurotoxicity**

1. Inter-Dependence of Developmental Domains: Neuropsychological Deficits and Psychosocial Risk

- Children with congenital heart disease are at increased risk of psychosocial risk (reduced quality of life, poor peer relationships, mood disorders)
- Children with CHD show a distinctive set of neuropsychological deficits
  - cognitive processing speed reduced
  - executive function deficits (working memory, shifting)
  - social cognition, emotion recognition deficits (self and other)
  - higher-order language deficits (pragmatic skills)

Why Might Peer Interactions be Challenging for Adolescents with CHD?

- Characteristics of Adolescent Interaction
  - conversation rapid-paced, short-hand references
  - highly affect-laden
  - allegiances shift rapidly and need to be updated in order to avoid faux pas
  - frequent use of language that is pragmatically complex (sarcasm, innuendo, insult, cajoling, deception, indirect communications)

Peer Interactions in Adolescence

- **Characteristics**
  - conversation fast-paced, telegraphic references (rapid information processing)
  - highly affect-laden (need to be able to identify accurately and rapidly the affective meaning of facial expressions and language)
  - allegiances shift rapidly and need to be updated in order to avoid faux pas (need good cognitive flexibility and working memory)
  - frequent use of language that is pragmatically complex (sarcasm, innuendo, insult, cajoling, deception, indirect communication) (need to be able to read others' emotions and intents and be able to see things from another's perspective)

2. Developmental Cascades
Cincinnati Prospective Lead Study: Adjusted Rate Ratios (maternal IQ, gender, socioeconomic status, maternal education) for each 5 µg/dL increment in blood lead

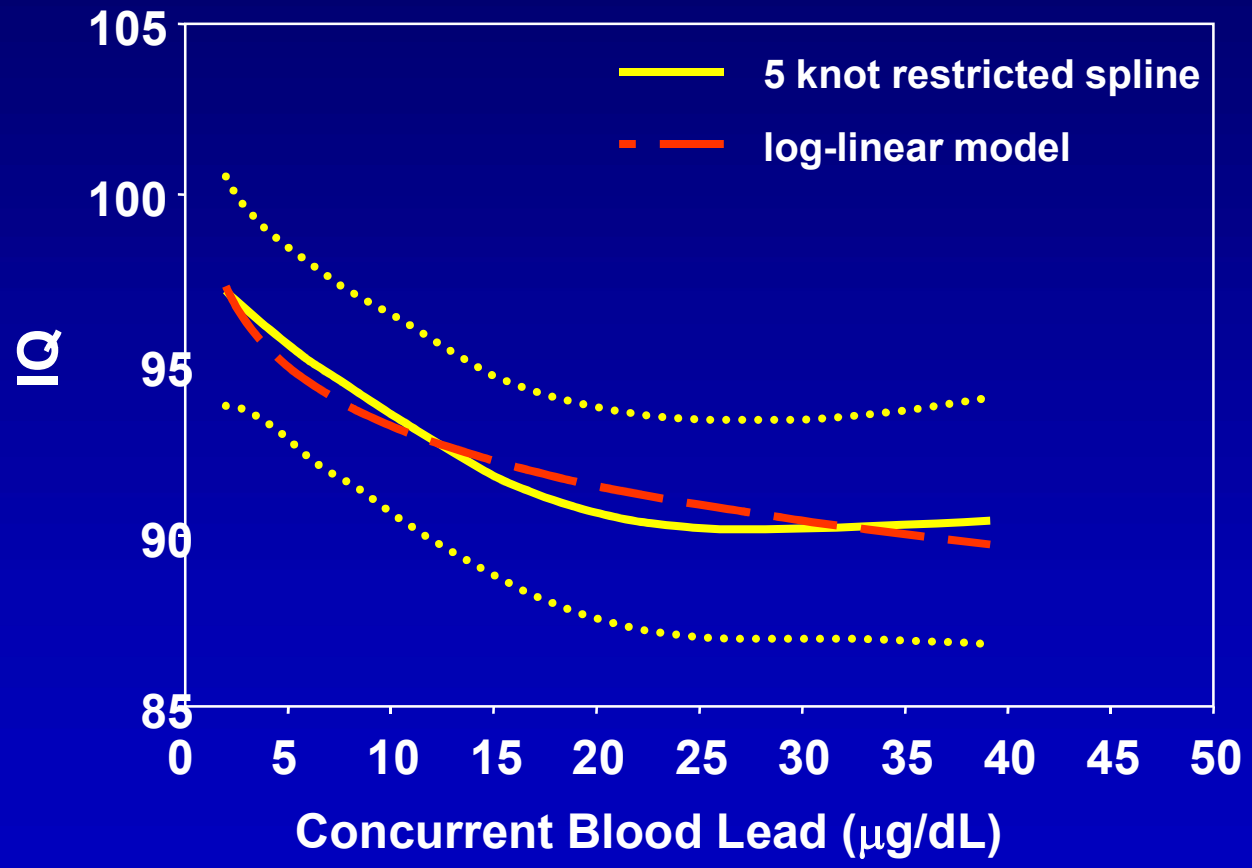
- **Total arrests:**
  - prenatal Pb: **1.40 (1.07-1.85)**
  - average childhood Pb: 1.07 (0.88-1.29)
  - 6-year blood Pb: **1.27 (1.03-1.57)**

- **Violent offenses:**
  - prenatal Pb: 1.34 (0.88-2.03)
  - average childhood Pb: **1.30 (1.03-1.64)**
  - 6-year blood Pb: **1.48 (1.15-1.89)**

Wright et al. *PLoS Medicine* 2008;5(5):e101

Relationship of Concurrent Blood Lead Level and IQ:

Lanphear et al. *Environ Health Perspect* 2005;113:894-899



Blood Lead Levels and Performance on End-of-Grade Reading Achievement Test, 2000-2004, NC 4th graders (N=8,600)

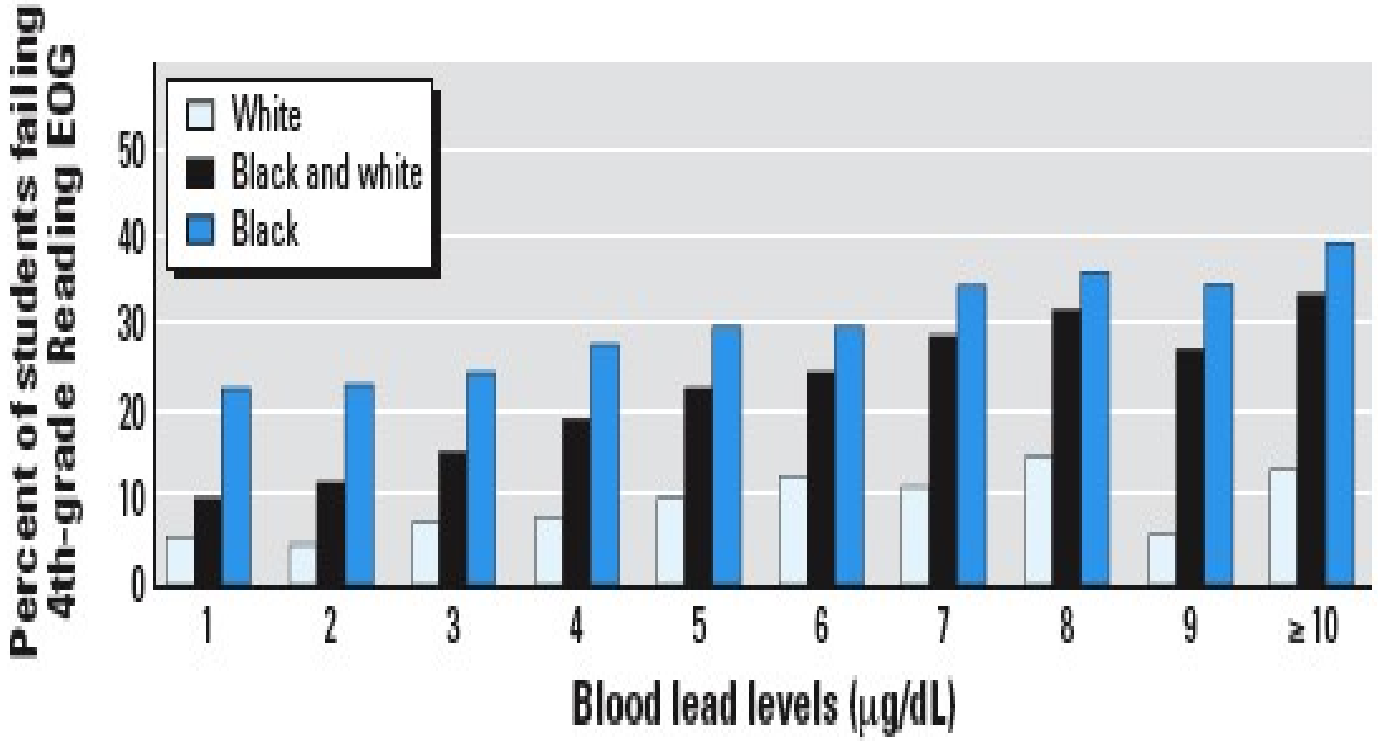
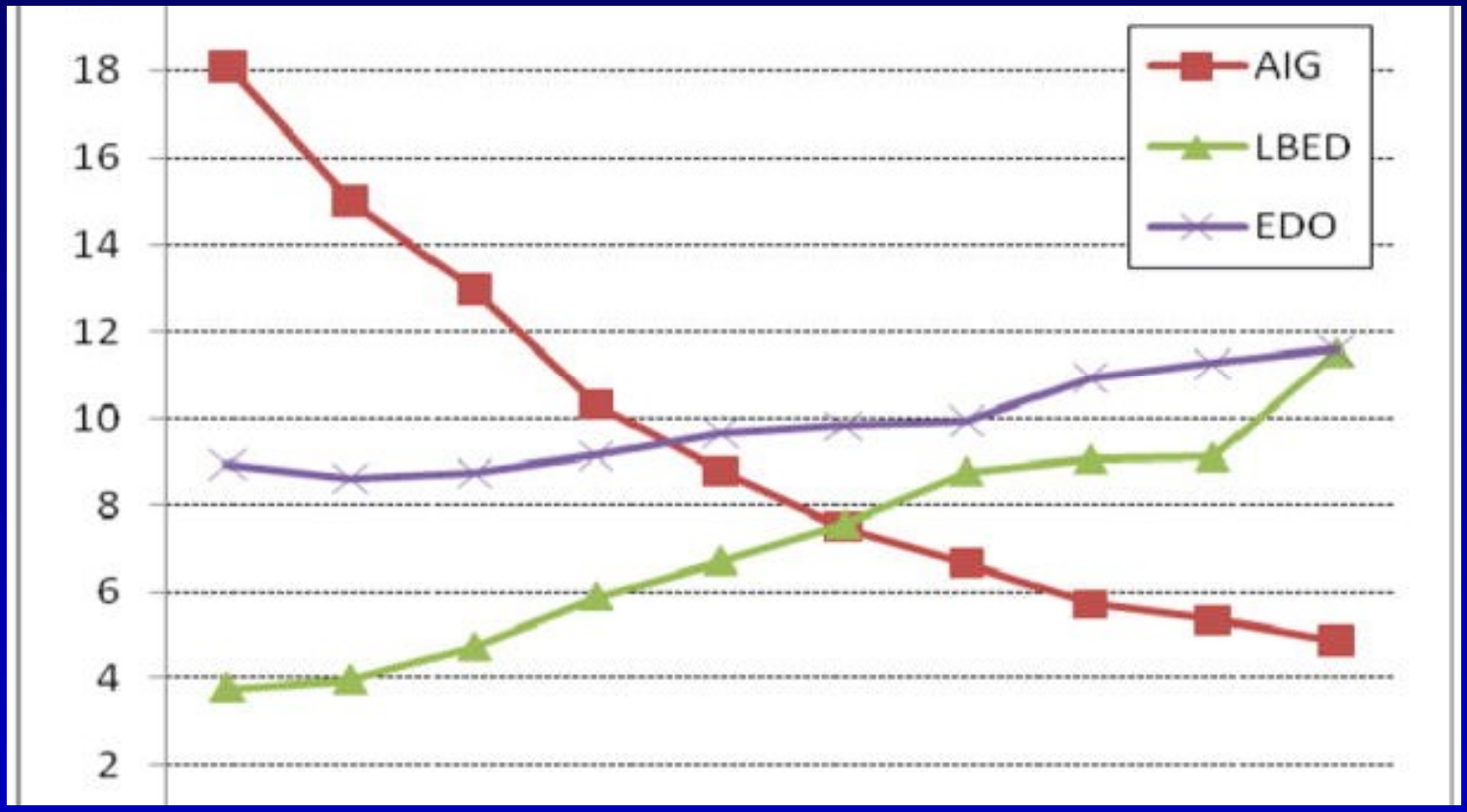


Figure 4. Percent of students failing 4th-grade Reading EOG.

Miranda et al., *Environ Health Perspect* 2007;115:1242-1247

Blood Lead Level and "Exceptionality Designations" in 4th Graders (NC) (Miranda et al. Int J Child Health Hum Dev 2010:3:77-84)



AIG: advanced and intellectually gifted
LBED: learning and behavioral exceptional
EDO: designated exceptional for other reasons (sensory, physical, ASD, severe IDD)

Blood Lead Level and ADHD: NHANES 1999-2002

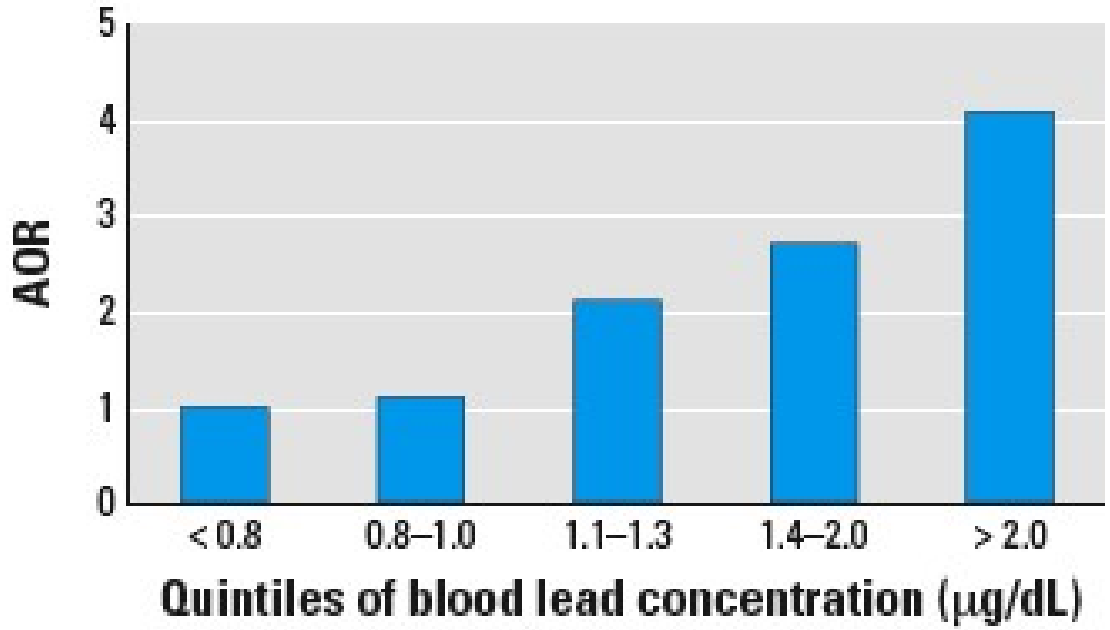
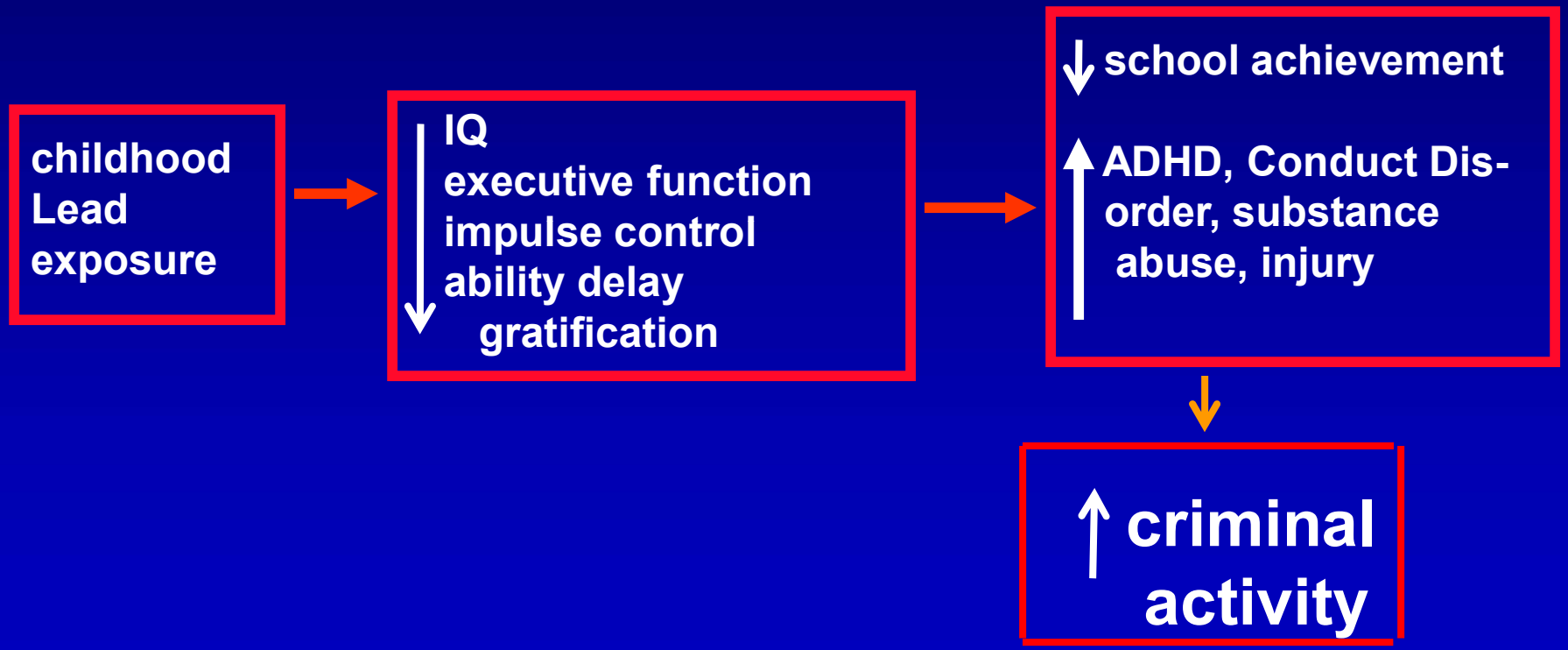


Figure 1. AOR for ADHD among U.S. children, NHANES 1999–2002, by blood lead concentration (µg/dL). The model was adjusted for child's age, sex, race/ethnicity, preschool attendance, serum ferritin, prenatal ETS exposure, smoker in the household, and insurance status.

p-value for trend = 0.012.

Braun et al. *Environ Health Perspect* 2006;114:1904-1909

Hypothesized Chain of Events Linking Childhood Lead Exposure to Adverse Psychosocial Outcomes in Adulthood



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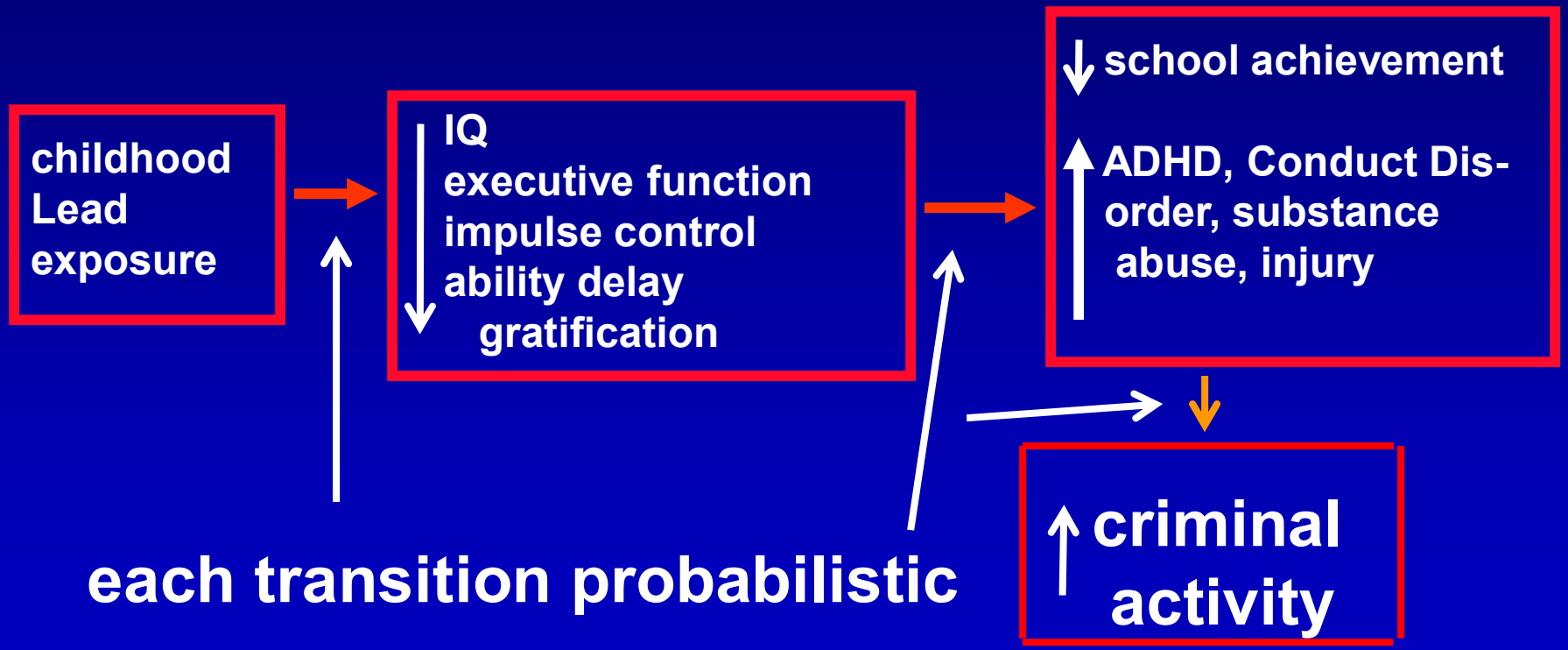


3. Silent or Delayed Neurotoxicity

- Damage not overtly expressed until it is uncovered by a later challenge by biological stressor (e.g., nutritional deficiency, medical condition or event, epigenetic change)

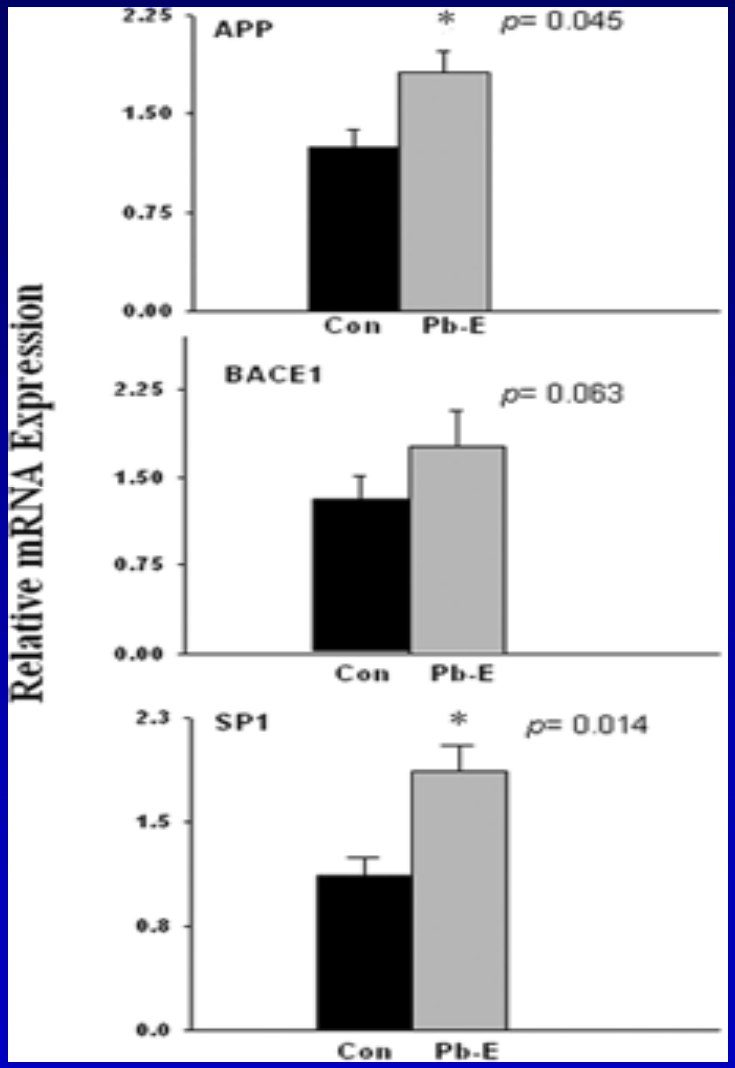
- Examples
  - Early lead exposure and schizophrenia (Opler et al., 2004, 2008); lead-induced hypoactivity of the NMDA subtype of glutamate receptor, combined with a genetic susceptibility (Guilarte et al., 2013; Stansfield et al., 2015)
  - Alteration of developmental programming, i.e., early-life epigenetic changes expressed as altered patterns of gene expression in later life

Rodent Studies of Early-Life Lead Exposure and Epigenetic Processes Related to Alzheimer's Disease
(Zawia et al. Free Radic Biol Med 2009; 46: 1241-9)

- AD characterized by extracellular deposition of beta-amyloid proteins (Aβ) and intracellular deposition of hyperphosphorylated tau protein

- at 20 months, rats exposed to lead only as newborns showed delayed overexpression, as adults, of the gene encoding the β-amyloid precursor protein (APP)
- increase in APP gene expression accompanied by an elevation in β-amyloid protein in brain tissue.
- same changes *not* seen in rats exposed to lead only as adults

Alzheimer's Disease-like Pathology in 23-year-old Monkeys After Developmental Exposure to Lead (Wu et al. *J Neurosci* 2008;28:3-9)



Increased mRNA expression of APP and BACE1 (ß-site APP cleaving enzyme), and Sp1 (transcriptional regulator) in frontal cortex

Increased intracellular staining of total Aß and dense core plaques (especially rich in Aß1-42, particularly amyloidogenic species)

20% reduction in activity of DNA methyltransferase 1 (suggesting latent gene expression effects mediated by pathways regulated by DNA methylation)

Higher levels of 8-oxo-dG (biomarker of oxidative DNA damage)

Boston Prospective Lead Study

- At follow-up (29 years of age), those with umbilical cord blood lead level > 10 µg/dL:
  - lower mean plasma $A\beta_{42}$ concentrations and lower $A\beta_{42}$:$A\beta_{40}$ ratio
  - inverse relationships between cord blood lead level and expression of 3 genes implicated in Aβ production and deposition in brain:
    - ADAM metallopeptidase domain 9
    - Reticulon 4
    - Low-density lipoprotein receptor-related protein associated protein 1

Mazumdar et al., *Environ Health Perspect* 2012;120:702-7

Other Human Studies

- Maternal patella lead levels associated with global DNA hypomethylation in newborns (Pilsner et al., 2009) and adult males (Wright et al., 2010)

- Childhood blood lead level associated with significantly lower DNA methylation at the differentially methylated region regulating PEG3 in adult peripheral blood (Li et al., 2016)

Principle 3

Early-life lead exposure likely has intra-familial and intergenerational impacts

A Transactional/Intergenerational Model of Child Development

- Child shapes his or her environment as well as being shaped by it
- In neurotoxicity studies, implicit assumption is that the influence is unidirectional, from environment to child only
- Effects of a neurotoxicant on child behavior can be mitigated or aggravated by responses the behavior elicits from significant others (parents, siblings, peers, teachers)
- Residual effects of neurotoxicant exposure influence parenting behaviors toward own offspring, creating potential for indirect effects on following generation
  - Animal models: perinatal phthalate exposure and poorer maternal care (nursing,grooming behaviors) (Rosenfeld, Front Neurosci 2015)

Principle 4

Early-life lead exposure constrain a child's ability to respond effectively to future insults or to future opportunities that would otherwise enhance neurodevelopment

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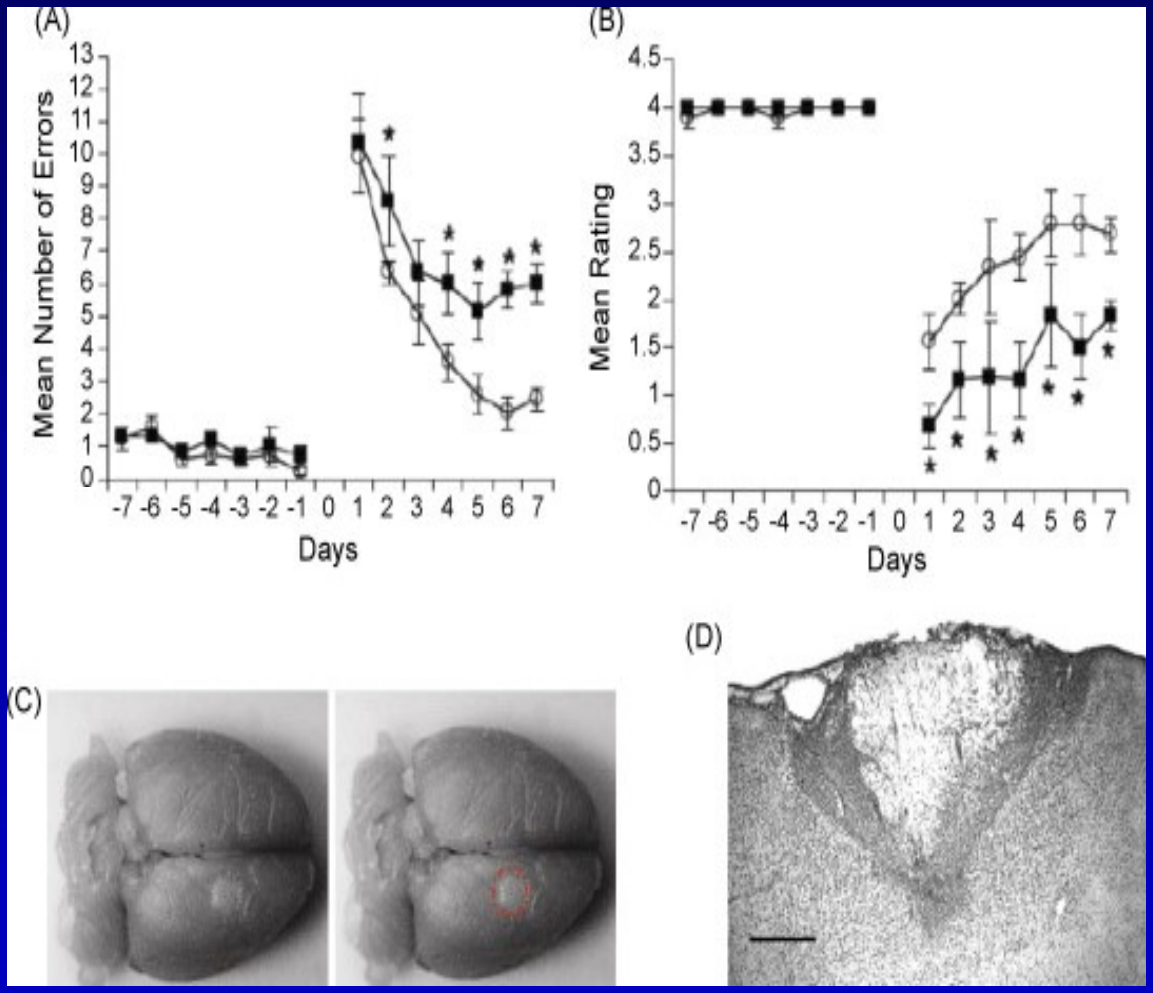
Deficits from early-life neurotoxicant exposure constrains a child's ability to respond effectively to future insults or to future opportunities that would otherwise enhance neurodevelopment

Early lead exposure functions as an effect modifier of a later insult, e.g., slope of the dose-response relationship, speed or extent of recovery

Later insult might be simply neurodegenerative processes associated with aging

- **Weiss et al. (2002) speculated that early neurotoxicant exposure influences manner in which genetic predispositions relevant to aging are expressed (reducing ability to compensate for neuronal loss, more quickly reaching stage at which clinical signs emerge)**

Impact of Early Lead Exposure on Effects of a Photothrombotic Stroke in Hind Limb Parietal Sensorimotor Cortex



Squares: Lead-exposed rats; A: beam walking; B: proprioceptive limb placing

Schneider JS, Decamp E. *Neurotoxicology* 2007;28:1153-1157

Lead exposure and development of columnar processing units in neocortex

- Early-life lead exposure:
  - produces dose-related reduction in barrel field area ($r = -0.74$; $P < 0.001$); mean barrel field area in the highest exposure group decreased 12% versus controls; total cortical area in the same sections not significantly different (Wilson et al., *PNAS* 2000;97:5540-5545)
  - impairs reorganization of barrel field cortex following whisker ablation, leaving clusters of de-nervated neurons active but useless

Relevant Human Studies

- Elderly men with higher bone lead levels showed greater cardiac autonomic dysfunction on high air pollution days (Park et al., 2008)
- Inverse dose-effect relationship between bone lead level and cognition steeper in men with Parkinson's Disease than controls (Weuve et al., 2013)
- More highly lead-exposed men lost cognitive skills at faster rate than less-exposed men of similar age (i.e., reduction equivalent to an additional years of aging) (Stewart and Schwartz, 2007)

Conclusions

- **“Studies should answer the important (but difficult) questions, even if only imprecisely, rather than trying to answer the less important (but easier) questions definitely” (Sexton and Linder, 2011)**

Implications for Study Interpretation and Policy

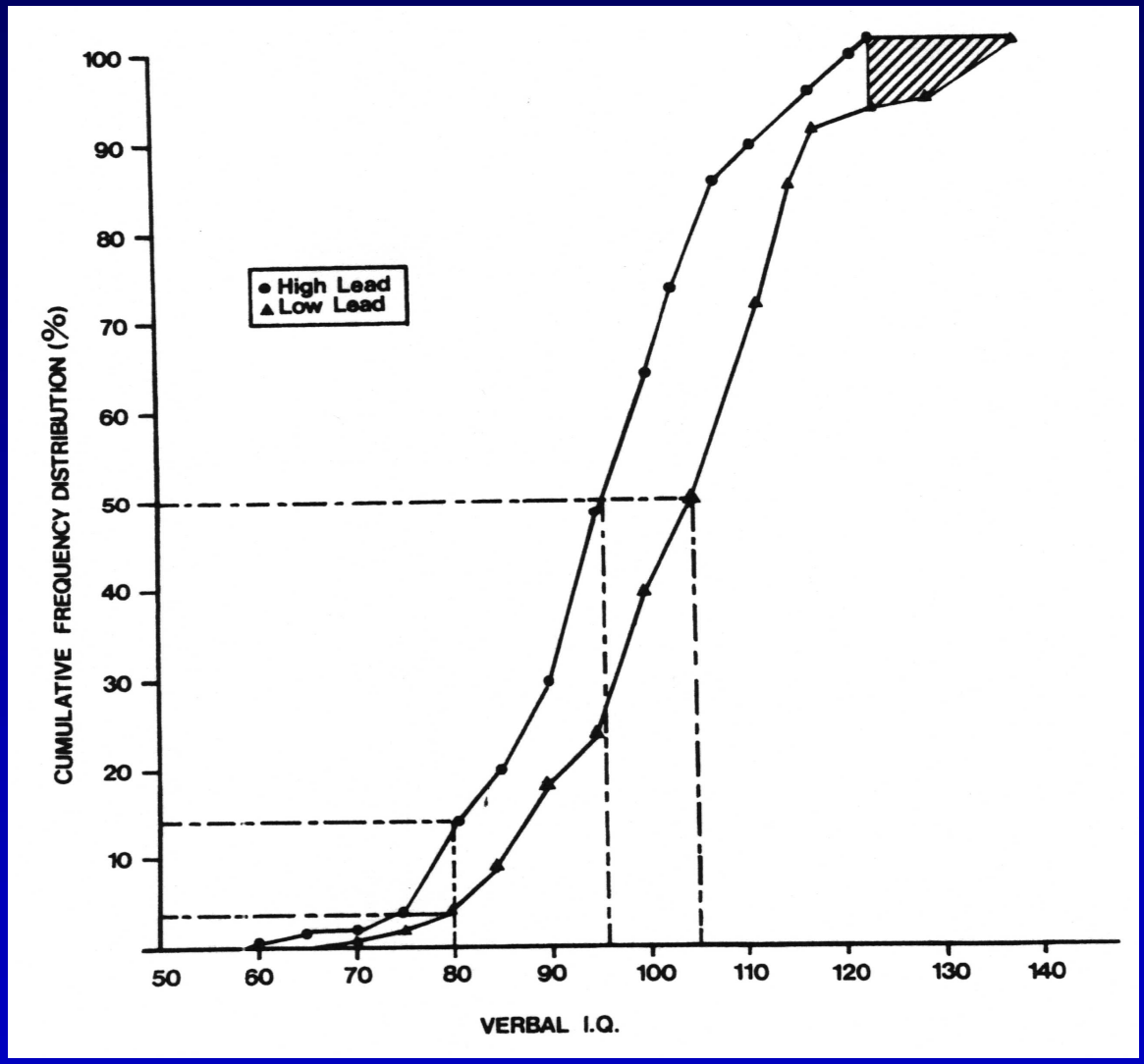
- Developmental perspective helps explain why poor children suffer disproportionately from neurotoxicants ("triple jeopardy")
  - more highly exposed
  - adverse impact of a given exposure is worse
  - renders them less resilient to later neurological insults and less able to benefit from environmental factors that support optimal development

Quantification of Disease Burden

- Implications for how we estimate burden of disease associated with lead
  - WHO global burden of disease estimate based solely on intellectual disability (IQ<70)

- Developmental approach would focus not only on near-term impacts such as reduction in IQ, but include downstream impacts that unfold over time as result of early perturbations of developmental trajectory
- Would also consider subclinical impacts that are more prevalent than “disease”

Cumulative Frequency Distributions of Children's Verbal IQ, Stratified by Tooth Lead Level



Needleman, Leviton, Bellinger *N Engl J Med* 1982;306;367

Childhood Lead Exposure

blood lead distribution, 1-5 year olds (NHANES, 2/2011):

50th	75th	90th	95th	98th
1.43	2.10	2.98	3.80	7.5

dose-effect assumptions (Lanphear et al., 2005):

- **slope over range 2.4-10.0 = -0.51 IQ pts/µg/dL (also assumed for range 0-2.4 µg/dL); -.19 pts/µg/dL over range of 10-20**
- **for children with blood lead level >10, assume mean of 15, and average IQ loss of 6.1 (5.1 + 1)**

IQ loss Attributable to Lead

•50%	0-1.43 µg/dL:	12,750,000 X 0.72 X 0.51	=	4,717,500
•25%	1.43-2.10:	6,375,000 X 1.77 X 0.51	=	5,737,500
•15%	2.1-2.98:	3,825,000 X 2.54 X 0.51	=	4,972,500
•5%	2.98-3.80:	1,275,000 X 3.39 X 0.51	=	2,205,750
•3%	3.80-7.50:	765,000 X 5.65 X 0.51	=	2,203,200
•2%	>7.5:	510,000 X 6.1	=	3,111,000

total IQ loss: 22,947,450 points

Calculation of IQ loss for Lead

- 50% 0-1.43 µg/dL: 12,750,000 X 0.72 X 0.51 = 4,717,500
- 25% 1.43-2.10: 6,375,000 X 1.77 X 0.51 = 5,737,500
- 15% 2.1-2.98: 3,825,000 X 2.54 X 0.51 = 4,972,500
- 5% 2.98-3.80: 1,275,000 X 3.39 X 0.51 = 2,205,750
- 3% 3.808-7.50: 765,000 X 5.65 X 0.51 = 2,203,200
- 2% >7.5: 510,000 X 6.1 = 3,111,000

total IQ loss: 22,947,450 points

Total IQ Losses Associated with Medical Events/Conditions, US Children 0-5 Years (Bellinger, *Environ Health Perspect* 2012; 120:501-7)

Event/Condition	Total Number of IQ points Lost
Brain tumors	37,288
Duchenne muscular dystrophy	68,850
Congenital heart disease	105,805
Chemotherapy (ALL)	135,788
Type 1 diabetes	185,640
MethylImercury	**1,385,785**
Pediatric bipolar disorder	2,203,200
Traumatic brain injury	4,856,086
Nonorganic failure to thrive	5,355,000
Autism spectrum disorders	7,018,563
Iron deficiency	9,409,510
ADHD	16,799,400
Organophosphate pesticides	**18,978,019**
Lead	**22,947,853**
Preterm birth	34,031,025

- **The problem of childhood lead poisoning, "…is so well-defined, so neatly packaged, with both causes and cures known, that if we don't eliminate this social crime, our society deserves all the disasters that have been forecast for it."**

Rene Dubos, 1969