Assessing the Evidence

George G. Rhoads, MD, MPH
Department of Epidemiology
UMDNJ School of Public Health

The opinions expressed in this talk are my own and do not necessarily reflect those of the CDC or its Advisory Committee on Childhood Lead Poisoning Prevention.

Evidence-based Public Health

- Interventions should be evidence based
- Good quality, peer reviewed data needed; contrary evidence taken into account
- Requires leadership to persuade our communities not to act on anecdotes, poorly defined clusters, & special interests
- Harder to implement than evidence based medicine

Challenges Encountered in Environmental Epidemiology

- Nearly all observational studies have some confounding.
- Exposure measurements are often poor.
- Relative risks of interest are usually small.
- Sometimes hard to distinguish *a priori* hypothesis testing from data dredging.
- Findings, however tentative, are often amplified by the press.

Example: Air Pollutants & SGA

- Air pollutants measured up to 10 km distant from address on birth certificate
- 4 pollutants measured in each of the three trimesters of pregnancy
- RR observed for pollutant increase from 25th to 75th percentile was 1.1 for NO_2 and $PM_{2.5}$
- Despite limitations, study got considerable press coverage

How Might We Strengthen the Evidence on Environmental Risks?

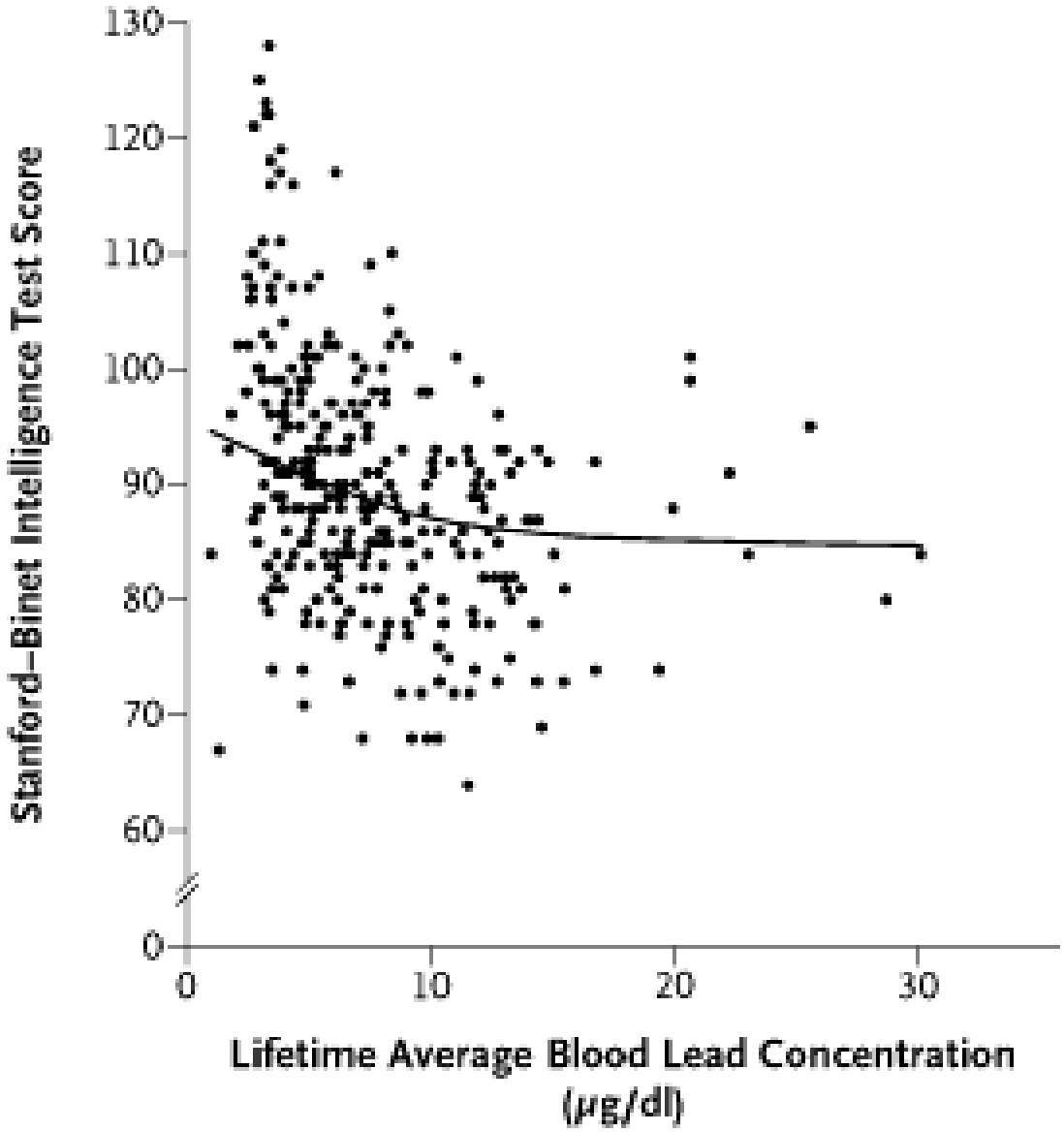
- Do more randomized prevention trials and quasi-experimental studies
- Use evidence available from secular trends in exposures and in health outcomes
- Employ more variation in study design to better control confounding in the design phase of our studies rather than depending so heavily on multivariate analysis

Example: Low Level Childhood Pb Exposure

- Recent studies have detected Pb effects on IQ at blood Pb <10 ug/dL
- Apparent strength of association is greater at blood Pb < 10 ug/dL

Potential for Confounding

- All studies relating blood lead to neurodevelopment of children are observational and could be biased by differences between highly exposed and less exposed children.
- Although many factors are statistically adjusted, it is impossible to be sure that this eliminates all important differences


Stanford–Binet Intelligence Test Score
130
120
110
100
90
80
70
60
0
0
10
20
30
Lifetime Average Blood Lead Concentration
(μg/dl)

Adj. Decrease in IQ per 1 ug/dL Blood Lead (Age 3) – Canfield et al

Lead Measure	All Children N= 172	Blood Lead <10 ug/dL N= 101
Lifetime Mean	0.35	1.22
Concurrent at Age 3	0.31	1.36

Change in Mean Blood Lead in U.S. 1-5 Year Old Children

NHANES Data

YEAR	MEAN VENOUS BLOOD LEAD
1976-80	15.0 ug/dL
1988-91	3.6 ug/dL

Predicted Improvement in IQ in 3 Year-olds in 1980's Based on Data of Canfield

Pop Blood Lead Change: 15.0 → 3.6 ug/dL

15→10 @ 0.31 = 1.5 IQ Points

10→3.6 @ 1.36 = 8.7

10.2 IQ Points

NHANES III Analysis

Lanphear et al, 2000

- National sample of 4816 children aged 6-16 evaluated at one visit
- Venous blood lead collected
- School achievement recorded
- Children completed several measures of psychological function

Adj. Decrease in WRAT per 1 ug/dL Blood Lead (Ages 6-16),

Lanphear et al, NHANES III Data

Wide Range Achievement Test-Revised (Mean = 100 S.D. = 15)	All Children N= 4853	Those with Blood Lead <7.5 ug/dL N= 4526
Reading Subtest	0.99	1.53
Arithmetic Subtest	0.70	1.06

Predicted Improvement in Reading in 9 Year-olds in 1980's Based on Cross Sectional Analysis of NHANES III Data

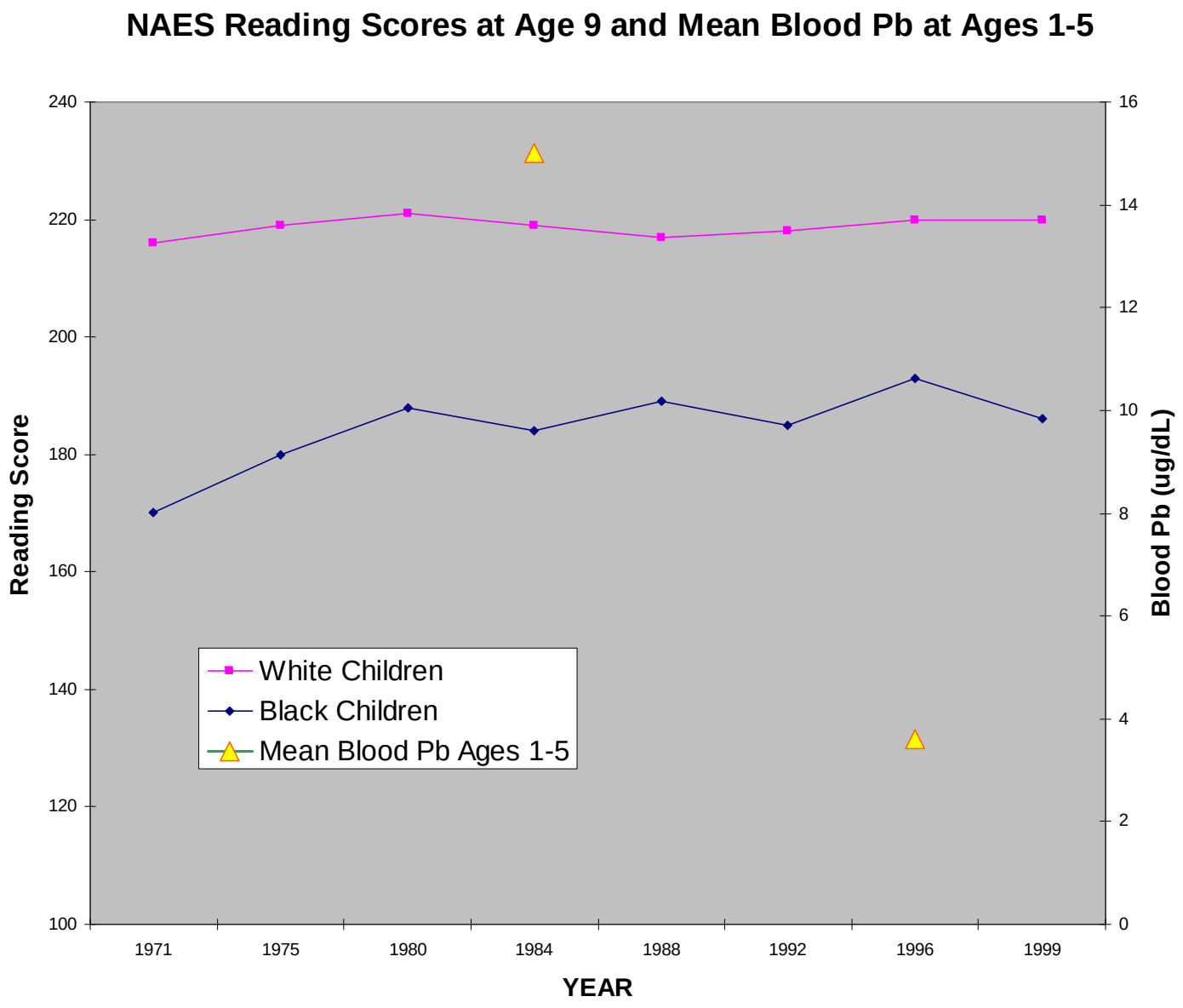
Pop Blood Lead Change: 15.0 → 3.6 ug/dL

Predicted Change in WRAT Reading Score

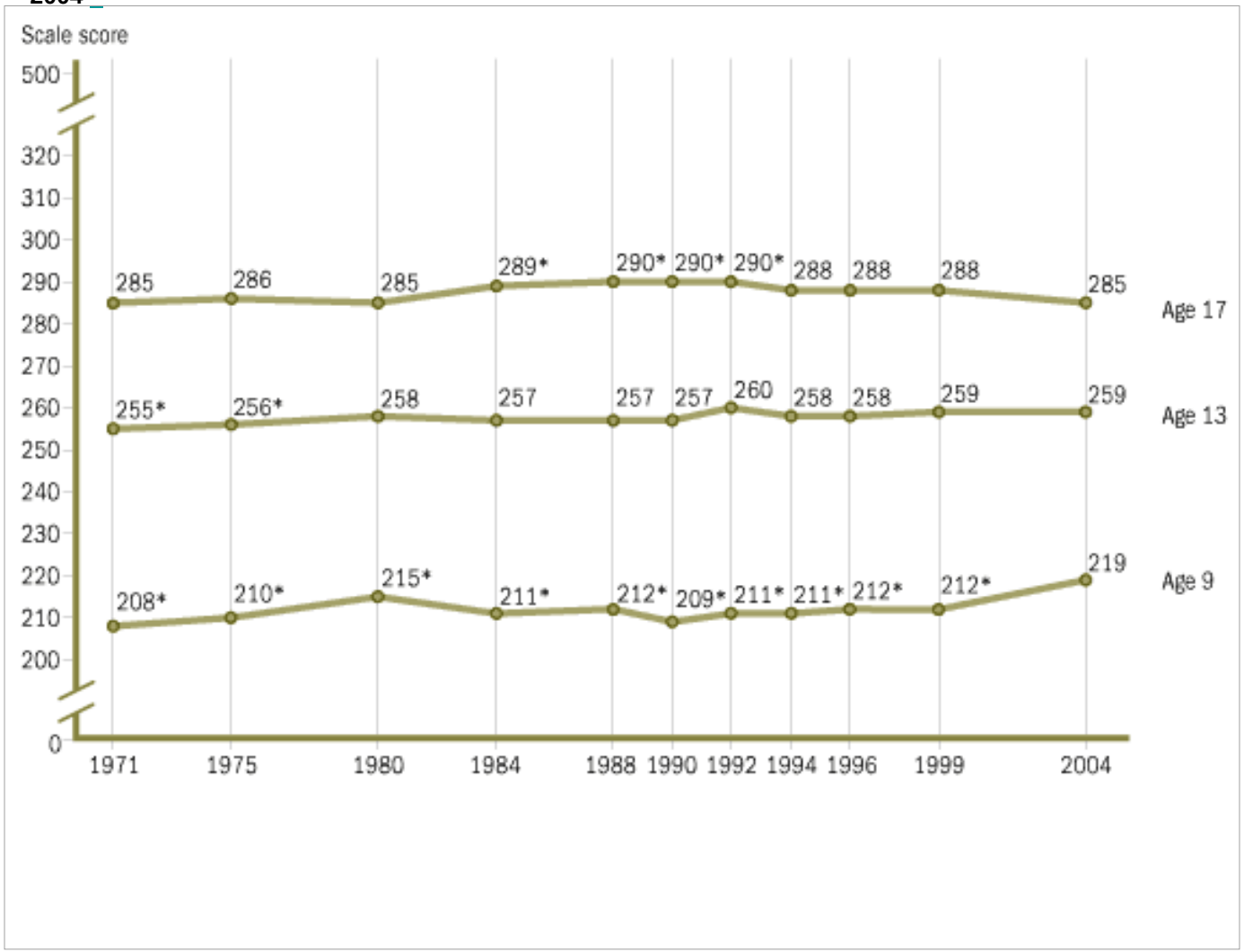
15→7.5 @ 0.99 = 7.4

7.5→3.6 @ 1.53 = 6.0

13.4


NAES Reading Scores at Age 9 and Mean Blood Pb at Ages 1-5
Reading Score
Blood Pb (ug/dL)
YEAR
240
220
200
180
160
140
120
100
16
14
12
10
8
6
4
2
0
1971
1975
1980
1984
1988
1992
1996
1999
White Children
Black Children
Mean Blood Pb Ages 1-5

Trends in average reading scale scores for students ages 9, 13, and 17: 1971–2004



* Significantly different from 2004.
SOURCE: U.S. Department of Education, Institute of Education Sciences, National Center for Education Statistics, National Assessment of Educational Progress (NAEP), selected years, 1971–2004 Long-Term Trend Reading Assessments.

Potential for Reverse Causality

- Children with less intellectual potential may have more hand-to-mouth activity (those with mental retardation are known to be at increased risk for Pb exposure)
- Parents who minimize lead exposure may also provide a better learning environment

Thought Experiment (1)

- Suppose, for a moment, an association between slow development and ingestion, or poor parenting and ingestion opportunity that is independent of any lead effect.
- Suppose further a comparison of two groups of children, one with more ingestion and lower IQ potential and the other with less ingestion and higher IQ potential. Let’s say the IQ difference between the two groups is 3 points.

Thought Experiment (2)

Then:

- In a high lead environment children with low potential or poor parenting will have substantially higher blood leads than other children because the extra ingestion will include a lot of lead. To illustrate, let's say 9 ug/dL.
- In low lead environments the blood lead difference between the same two groups of children will be slight. Let's say 3 ug/dL.

Thought Experiment (3)

Then:

- In a high lead environment we have 3 IQ points associated with a blood lead difference of 9 ug/dL which is 0.33 IQ points per 1 ug/dL blood lead.
- In a low lead environment we have 3 IQ points associated with a blood lead difference of 3 ug/dL which is 1.00 IQ points per 1 ug/dL blood lead.
- The numbers are arbitrary, but they illustrate how the bias might operate.

Summary

- Nationwide quasi-experiment has shown no evidence of effects predicted by recent observational studies of blood PB <10 ug/dL
- Observational studies relating blood Pb to developmental outcomes are likely to reflect at least some confounding or reverse causality
- For these reasons and several others lowering the level of concern below 10 ug/dL should await better evidence
- New observational designs or, preferably, a randomized prevention trial will be needed

Where Do We Need to Go

- Do more randomized prevention trials and quasi-experimental designs
- Examine consistency of conclusions with secular trends in exposure and outcome
- Improve exposure measurements and other features of study quality
- Make clear distinctions between *a priori* hypothesis testing and hypothesis generating studies

Thank You

for Your Attention

Common Weaknesses in Evidence

- No randomized prevention trials
- Observational studies all of similar design and subject to the same confounding
  - Esp socio-economic status
- Reviews fail to differentiate proven risks from those with limited or mixed evidence
  - e.g. Favorable time trends in exposure often ignored
- Multivariate analysis imperfect
  - May not completely control for a confounder
  - May even create an association that is not real

Stronger Blood Pb – IQ Relationship at <10 ug/dL Suggests Confounding

- Surprising finding obviously not widely predicted when level of concern was set at 10 ug/dL
- Exactly what one would predict under a scenario where children with less IQ potential had

  more hand-to-mouth activity, or

  more opportunity to ingest non-foods