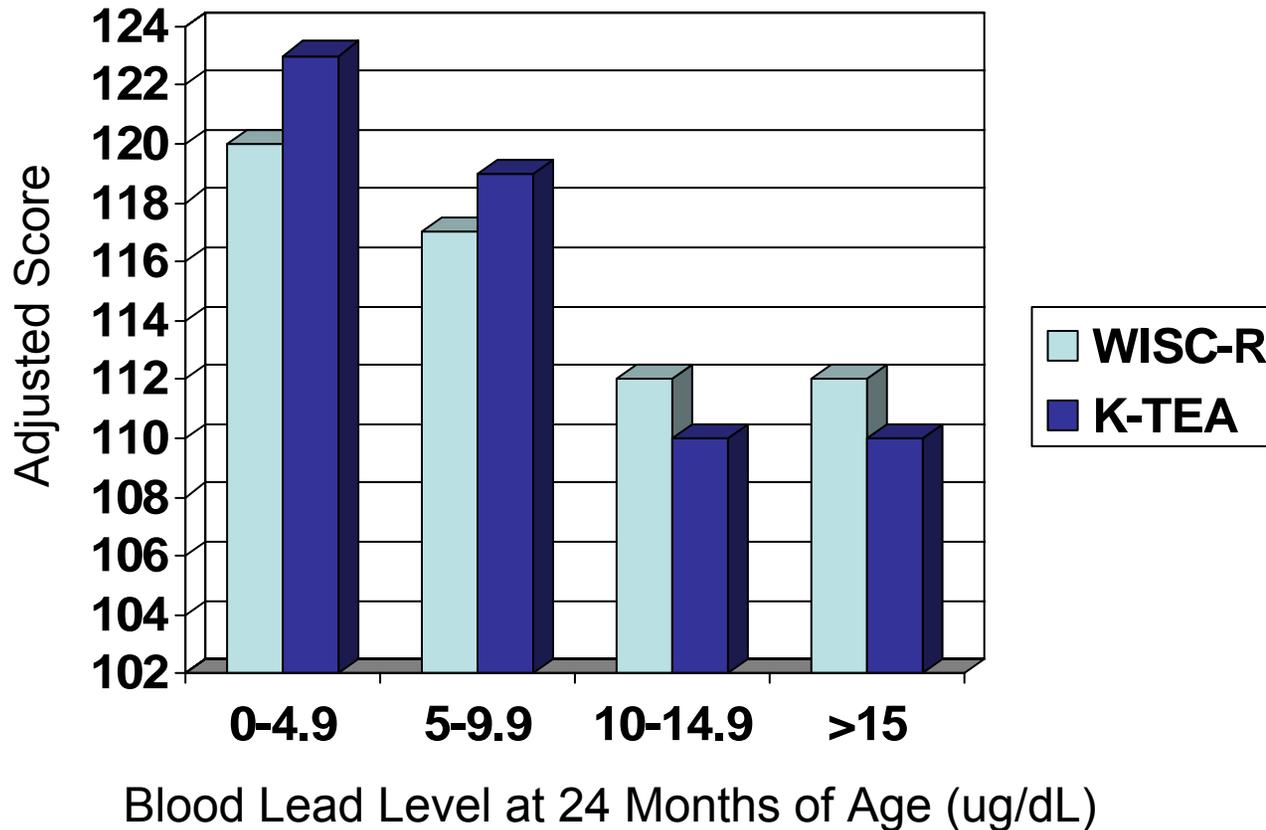


The Boston Prospective Study



Bellinger, et al. (1992), Pediatrics

Seeking Sensitive Periods

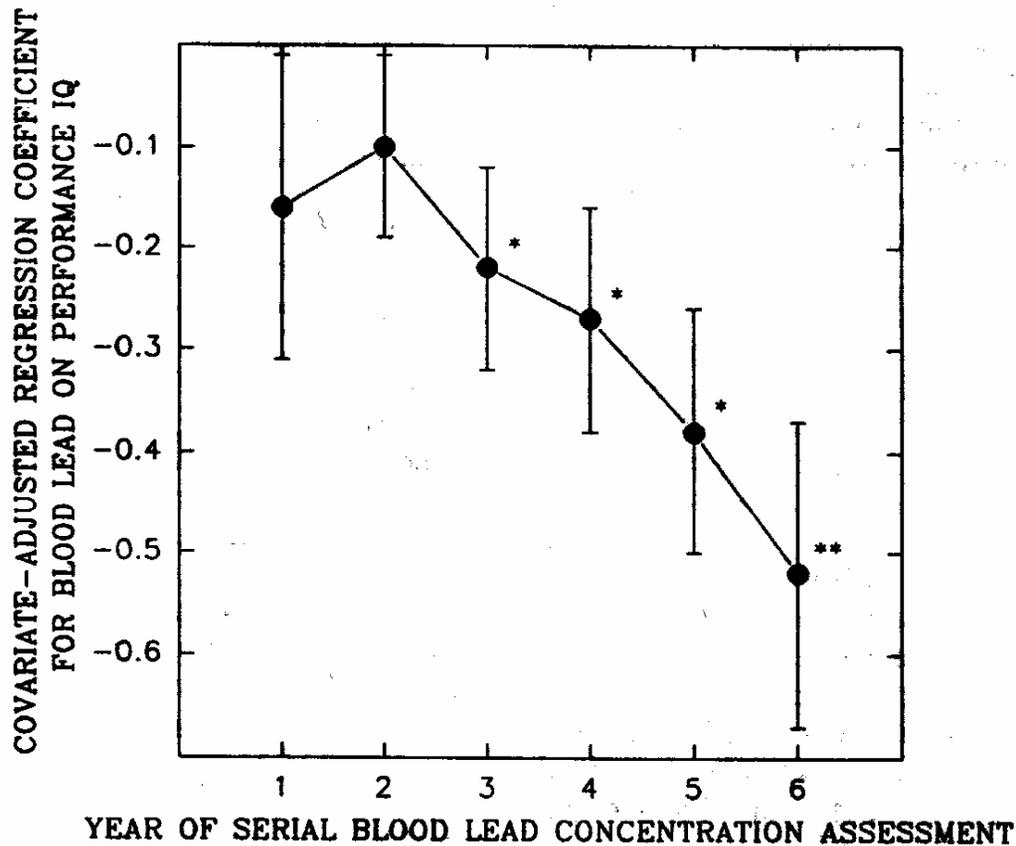


FIG. 1. Plot of covariate-adjusted regression coefficients (and SEs) for mean blood lead concentration by year of assessment and Performance IQ as measured by the Wechsler Intelligence Scale for Children-Revised. Data were previously presented in ref. 6. * $p < 0.05$; ** $p < 0.001$.

Later Blood Lead Levels Predict School-Age Assessments of IQ: Port Pirie Cohort Study at 11-13 Years (Tong, et al 1996)

Table 5—Estimated regression coefficients (SE) in IQ points per unit of log blood lead concentration from simple and multiple regression analyses*

Time of blood sampling	Unadjusted			Adjusted†		
	Verbal IQ	Performance IQ	Full scale IQ	Verbal IQ	Performance IQ	Full scale IQ
Cord blood	-2.9 (1.3) (P=0.03)	-1.8 (1.6) (P=0.25)	-2.7 (1.4) (P=0.06)	1.0 (1.3) (P=0.43)	1.2 (1.8) (P=0.48)	1.2 (1.5) (P=0.41)
15 Months	-8.4 (1.3)	-5.2 (1.7)	-6.2 (1.5)	-2.9 (1.3) (P=0.03)	-0.6 (1.9) (P=0.76)	-1.8 (1.6) (P=0.24)
3 Years	-8.5 (1.5)	-9.4 (2.0)	-9.8 (1.7)	-2.6 (1.6) (P=0.11)	-4.2 (2.3) (P=0.07)	-3.8 (1.9) (P=0.05)
5 Years	-8.4 (1.3)	-7.2 (1.7)	-8.9 (1.5)	-3.7 (1.4) (P=0.01)	-3.7 (1.9) (P=0.06)	-4.0 (1.6) (P=0.02)
7 Years	-7.9 (1.3)	-8.6 (1.7)	-8.9 (1.5)	-2.8 (1.4) (P=0.05)	-3.8 (2.0) (P=0.06)	-3.4 (1.7) (P=0.04)
11-13 Years	-5.7 (1.3)	-6.2 (1.7)	-6.5 (1.4)	-2.4 (1.3) (P=0.06)	-2.0 (1.8) (P=0.12)	-3.1 (1.4) (P=0.04)
Lifetime average to age 3	-9.3 (1.8)	-7.8 (2.4)	-9.5 (2.1)	-4.6 (1.9) (P=0.03)	-3.2 (2.7) (P=0.23)	-4.3 (2.2) (P=0.06)
Lifetime average to age 5	-9.8 (1.9)	-8.6 (2.4)	-10.1 (2.1)	-5.0 (2.0) (P=0.02)	-4.4 (2.8) (P=0.10)	-5.1 (2.3) (P=0.03)
Lifetime average to age 7	-9.6 (1.9)	-8.7 (2.5)	-10.0 (2.2)	-4.3 (2.1) (P=0.03)	-4.3 (2.9) (P=0.14)	-4.6 (2.4) (P=0.06)
Lifetime average to age 11-13	-10.8 (1.6)	-10.8 (2.2)	-11.6 (1.9)	-3.9 (1.8) (P=0.03)	-4.7 (2.6) (P=0.07)	-4.3 (2.1)‡ (P=0.04)

*All simple regression coefficients except for cord blood lead concentration were significant ($P < 0.001$); P values shown in parentheses are for multiple regression analyses.

†Adjusted for covariates described in the text.

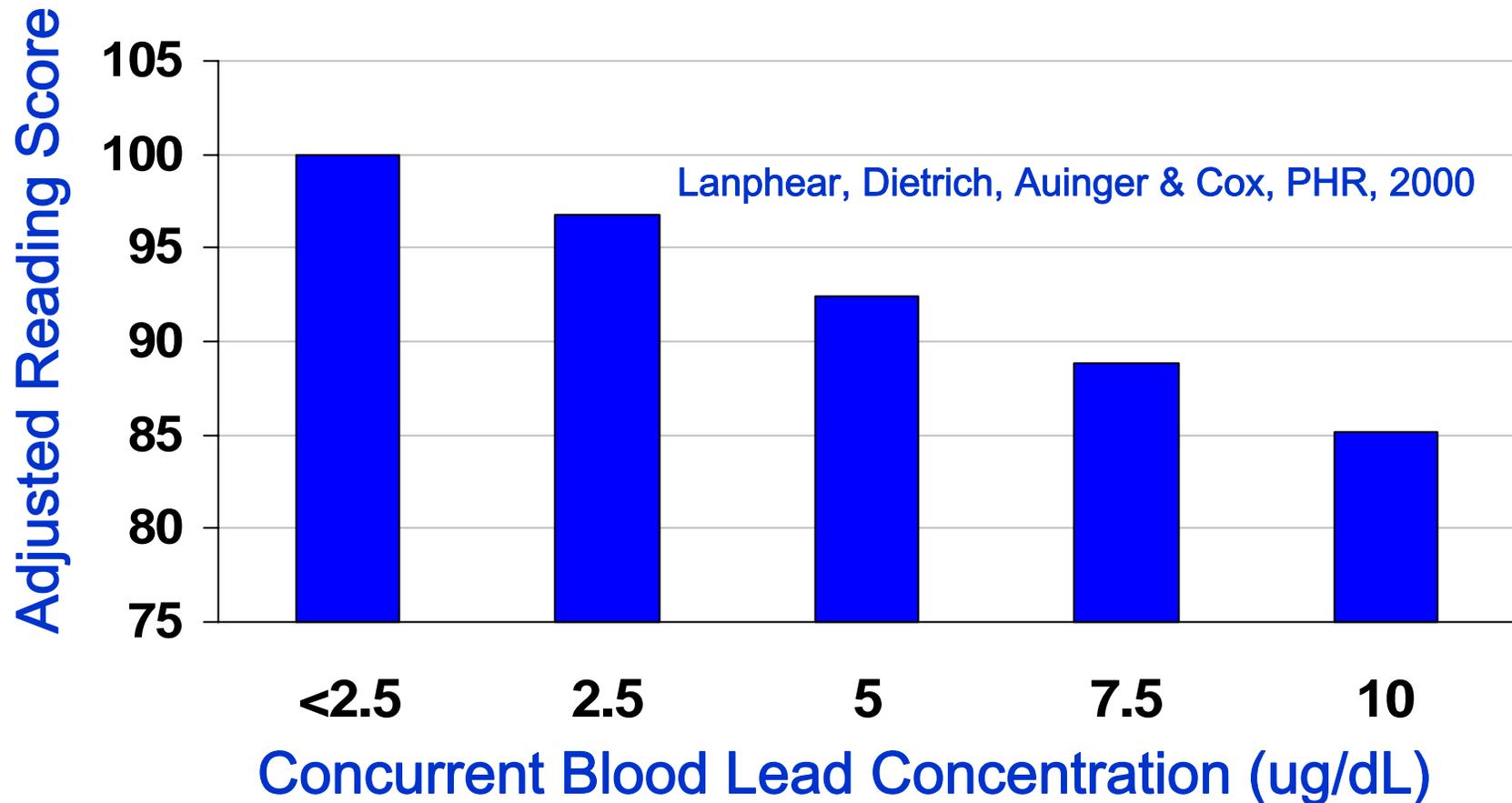
‡Analyses were based on the unit of natural log blood lead concentration in $\mu\text{g/dl}$; this means that the expected deficit in full scale IQ associated with a doubling of lifetime average blood lead concentration—for example, from 0.48 to 0.97 mmol/l (10 to 20 $\mu\text{g/dl}$) is 3.0 points: $4.3 \times (\ln[20] - \ln[10]) = 3.0$.

2y and 7y PbB on 7y IQ

PbB ($\mu\text{g}/\text{dL}$)		n	7y IQ Mean	7y IQ Comparison
2y	7y			
<24.9	<7.2	187	89	referent
<24.9	≥ 7.2	114	85	-3.6 (-6.4, -0.7)
≥ 24.9	<7.2	121	89	-0.0 (-2.8, 2.7)
≥ 24.9	≥ 7.2	195	84	-3.7 (-6.2, -1.3)

All adjusted for center, race, sex, language, parent's education, employment, single parent, caregiver's IQ and age at both PbB tests

Blood Lead Concentration and Reading Scores: NHANES-III (6-16 Years)

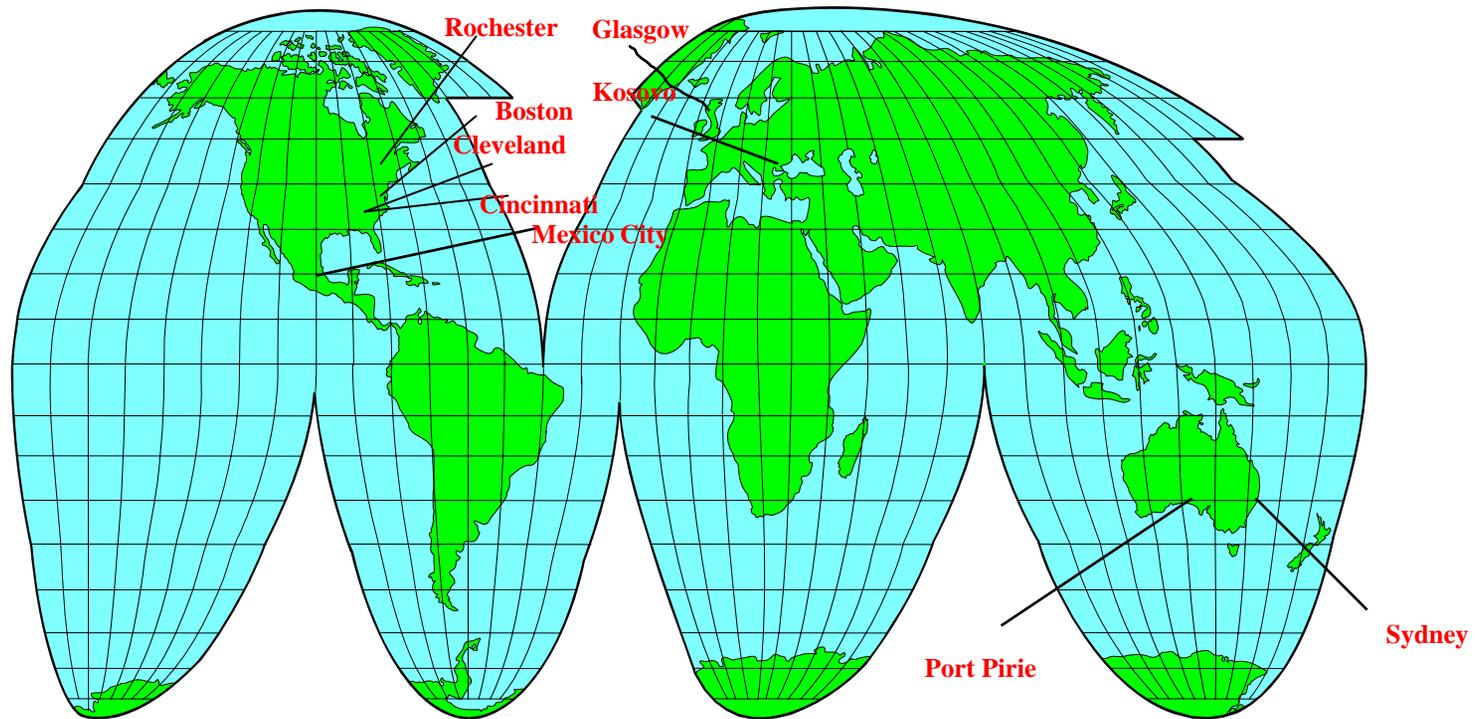


Low-level Environmental Lead Exposure and Children's Intellectual Function

An International Pooled Analysis of Prospective Studies

Lanphear, B.P. et al. (2005), Environmental Health Perspectives, 113, 894-899.

The International Prospective Studies of Lead and Child Development



Boston (Bellinger, et al.)
Cincinnati (Dietrich, et al.)
Cleveland (Ernhart, et al.)
Glasgow (Moore, et al.)
Kosovo (Graziano, et al.)

Mexico City (Rothenberg, et al.)
Port Pirie (Baghurst, et al.)
Rochester (Lanphear, et al.)
Sydney (McBride, et al.)

Objectives

- To examine the relationship between IQ and blood lead concentration in children followed prospectively, from infancy through 5 to 10 years of age.
- To test for evidence of lead-associated decrements in IQ scores at blood lead levels below 10 $\mu\text{g}/\text{dL}$.
- To test whether the lead-associated IQ deficit was greater for a given change in exposure for children with lower peak blood lead concentrations.

Blood Lead Variable Definition

Peak Blood Lead

Maximum blood lead of blood lead tests taken at 6 months, 1 year (or 15 month), 2, 3, 4, 5, 6, 7 year values

Early Childhood Blood Lead

Mean blood lead from 6 to 24 months

Mean Lifetime Average

Mean blood lead level from 6 month to concurrent value

Concurrent Blood Lead

Blood lead value at age concurrent with IQ testing or otherwise closest to IQ testing for each site.

The Relationship of IQ vs Selected Blood Lead Indices Adjusted for All Available Covariates

Variable	Concurrent (R ² =0.630)		Peak R ² =0.628)		Early Childhood (R ² =0.631)		Lifetime Average (R ² =0.629)	
	β	p value	β	p value	β	p value	β	p value
log blood Pb	-2.58	<.001	-2.79	<.001	-2.09	0.001	-2.97	<.001
HOME Score (z-score)	4.23	<.001	4.30	<.001	4.32	<.001	4.28	<.001
Maternal IQ	4.77	<.001	4.88	<.001	4.98	<.001	4.88	<.001
Maternal education	1.12	0.016	1.14	0.014	1.17	0.012	1.11	0.017
Birth weight (per 100 g)	1.53	<.001	1.53	<.001	1.48	<.001	1.51	<.001
Birth order	-0.44	0.275	-0.44	0.275	-0.46	0.252	-0.44	0.275
Child's Sex	0.46	0.486	0.46	0.489	0.44	0.511	0.46	0.493
Marital status	1.15	0.259	1.00	0.328	1.10	0.437	0.99	0.333
Maternal age	0.13	0.768	0.18	0.675	0.21	0.761	0.17	0.701
Smoking (Y/N)	-0.08	0.915	-0.06	.938	0.03	0.974	-0.05	0.947
Alcohol (Y/N)	0.74	0.401	0.40	0.707	1.08	0.227	0.81	0.361

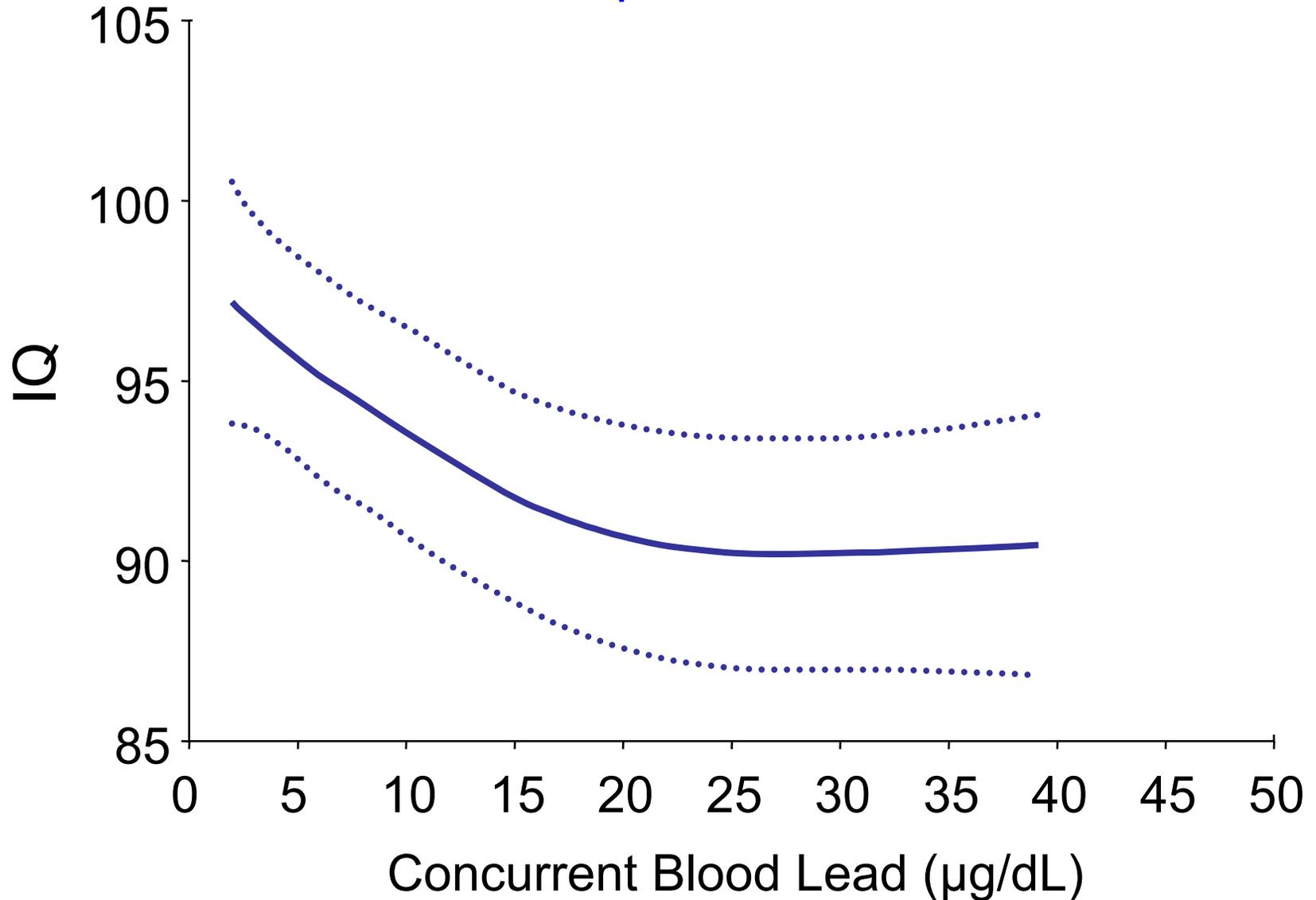
In summary,

- There is not strong support for a specific age (like 2 y) or a specific number (10, 5, 1) at which we can pinpoint when lead toxicity will or will not occur
- Rather, the data are more consistent with an “area under the curve” or “higher-longer” metric for exposure, with susceptibility continuing to school age anyway.

IQ – Outcome Variable

Site	Type IQ Test	Age at IQ Test
Boston	WISC-R	10
Cincinnati	WISC-R	7
Cleveland	WPPSI	5
Mexico City	WISC-R	7
Port Pirie	WISC-R	7
Rochester	WPPSI-R	6
Yugoslavia	WISC-R	7

Relationship of Concurrent Blood Lead Concentration with Children's Intellectual Function using a Restricted Cubic Spline Function



Conclusions

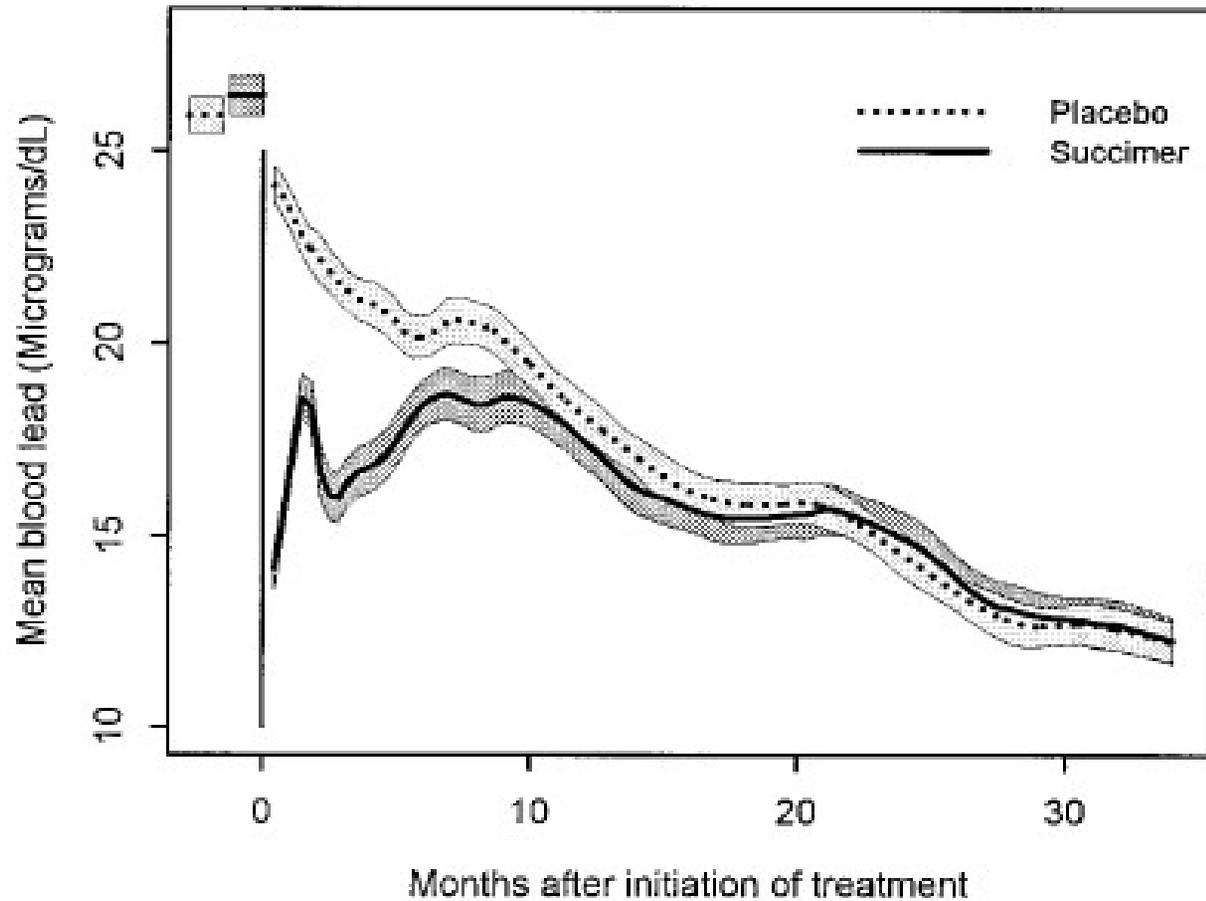
- Lead-associated intellectual deficits occur at concurrent blood lead levels below 10 $\mu\text{g}/\text{dL}$
- No evidence of a threshold for lead-associated intellectual deficits
- Sufficient evidence to mount an aggressive campaign to eliminate childhood lead exposure

Beyond Infancy

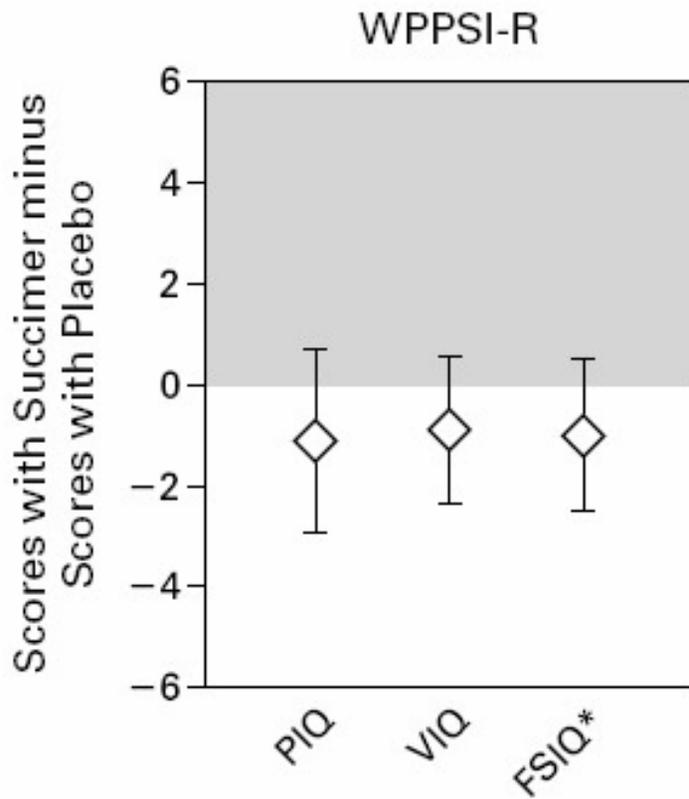
The pruning and reorganization of cortical areas is a protracted process that lasts well into the second decade of life. Given the extended maturation of the brain it is not surprising that it is more susceptible to functional damage and resulting developmental dysfunction.

Seyffert & Silva, Current Pediatric Reviews, 2005

Blood lead level in TLC study

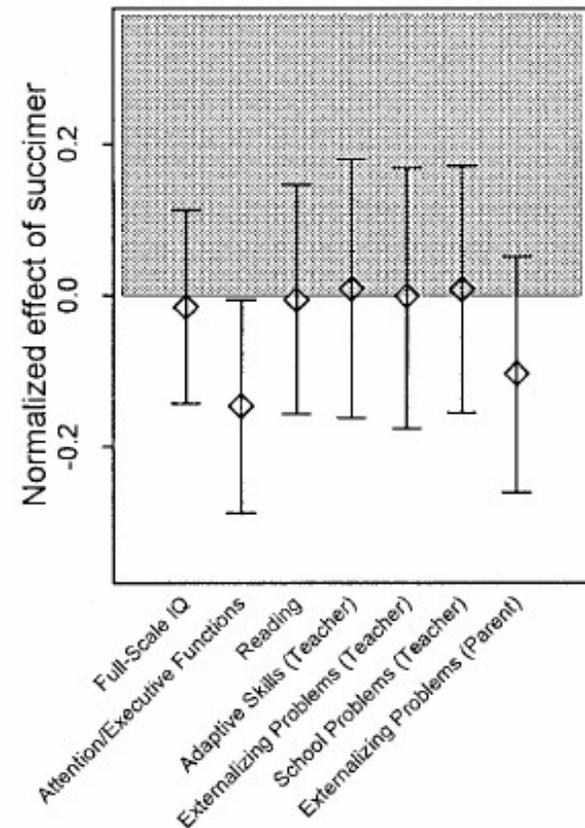


No IQ difference from treatment



36 mo follow-up

60 mo follow-up



5y and 7y PbB on 7y IQ

PbB ($\mu\text{g}/\text{dL}$)		n	7y IQ Mean	7y IQ Comparison
5y	7y			
<11.4	<7.2	244	89	referent
<11.4	≥ 7.2	52	86	-2.3 (-5.9, 1.3)
≥ 11.4	<7.2	62	88	0.3 (-3.1, 3.7)
≥ 11.4	≥ 7.2	255	84	-3.8 (-6.0, -1.6)

All adjusted for center, race, sex, language, parent's education, employment, single parent, caregiver's IQ and age at both PbB tests

Covariates

- Child's sex
- Birth order
- Birth weight
- Maternal IQ
- Maternal education
- Maternal age at delivery
- Marital status
- Prenatal smoking
- Prenatal alcohol use
- HOME Score