NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP MONOGRAPH ON HEALTH EFFECTS OF LOW-LEVEL LEAD

June 13, 2012

APPENDIX A:
HUMAN STUDIES OF NEUROLOGICAL EFFECTS OF LEAD CONSIDERED IN DEVELOPING CONCLUSIONS

Office of Health Assessment and Translation

Division of the National Toxicology Program

National Institute of Environmental Health Sciences

National Institutes of Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Cross-sectional Al-Saleh, (2001) Saudi Arabia	533 Saudi Arabian girls (6-12 yrs of age) enrolled in 33 public schools in Riyadh. Year not stated Male=0%	7.8 (0.9) yrs	8.11 (3.50) Measured at time of testing.	Standardized tests of cognitive, visual-motor, visual-perceptual functions (the Test of Non-Verbal Intelligence (TONI), and the Beery Visual Motor Integration (Beery VMI) and class rank as a measure of academic achievement	Spearman rank correlation analysis; Kruskal-Wallis one way analysis of variance; multiple regression analysis Sociodemographic variables, early developmental milestones and child health status.	Multiple regression on blood Pb levels and neuropsychological and academic achievement scores <u>Beery VMI Saudi-based Standard scores</u> **log Pb β(SE)= -5.16 (2.09); p=0.014** <u>Rank percentile scores</u> **log Pb β(SE)= -12.31 (2.85); p=0.0015** New text - Authors state that Pb had no effect on TONI scores for the entire population In regression analysis of girls with blood Pb ≤9, only class rank was associated with blood Pb levels (<0.02). In regression analysis of girls with blood Pb >9, class rank, VMI, and TONI scores were all associated with blood Pb levels (<0.05)	Blood Pb was significantly associated lower neurocognition scores and academic achievement in 6 to 12 year old girls.
Prospective Al-Saleh (2009) Al-Kharj, Saudi Arabia	Children of healthy Saudi mothers delivering at King Khalid Hospital Year= 2004; % male not stated	Cord n = 119 6 mon n = 107 12 mon n = 79 18 mon n = 56 24 mon n = 43	Prenatal: Cord: 2.73 (2.52) Postnatal 6 mon: 3.36 (2.38) 12 mon: 3.27 (2.02) 18 mon: 3.98 (1.06) 24 mon: 4.45 (2.31) Exposure measured at birth (cord), and at 6, 12, 18, 24 months when outcome was assessed	Early cognitive development assessed using the Bayley Scale of Infant Development (BSID-I), consisting of a Mental Developmental Index (MDI) and a Psychomotor Development Index (PDI).	Univariate analyses; Student's *t*-test, ANOVA, multiple regression analyses Infants age, weight, height, number of people living in the house, gestational age, head circumference, 1- and 5-minute Apgar scores, sibling rank, total number of siblings, total number of half-siblings	<u>Effects of prenatal Pb exposure:</u> **MDI at 6 months, β = -0.24; p=0.02** **PDI at 6 months, β= -0.23; p=0.02** MDI at 12 months, PDI at 12 months, MDI at 18 months, PDI at 18 months, and MDI at 24 months: not reported PDI at 24 months, β = -0.36; p=0.09 <u>Effects of postnatal Pb exposure (at 6 months):</u> MDI at 12 months, PDI at 12 months, MDI at 18 months, PDI at 18 months, and MDI at 24 months: not reported **PDI at 24 months, β = -0.57 (p=0.005)** Only β's and p-values for significant effects were reported.	Cord blood Pb was significantly associated with lower MDI and PDI at 6 months. Blood Pb at 6 months was significantly associated with lower PDI at 24 months.
Cross-sectional Altmann (1998) Germany	384 children in Duisburg (n=120), Leipzig (n=191), and Gardelegen (n=73) examined during regular medical examination for school entrance. Year =1994; Male = 52%	6.2 (0.425) Range: 5.0-7.8	Duisburg: 3.784 (0.140) Leipzig: 5.098 (0.153) Gardelegen: 3.206 (0.141)	Visual function assessed by neurophysiological measures of visual-evoked potentials (VEP) of three different checkerboard patterns (VEP1, VEP2 and VEP3) by peak latencies (N75, P100, N150), amplitude (Amp) and interpeak	Linear regression. Latencies adjusted for area, age, birth weight, head circumference, visual acuity, quality of fixation, and weight. Amplitudes adjusted for gender, head circumference, weight, quality of fixation	<u>Multiple regression for neurophysiological outcomes and log blood Pb (µg/L)</u>: Reg. Coeff. (SE), *p*-value VEP1N75 (n=336): 0.086 (0.059), *p*=0.144 VEP1P100 (n=336): -0.094 (0.058), *p*=0.107 VEP1N150 (n=329): -0.108 (0.059), *p*=0.070 VEP1Amp (n=324): -0.015 (0.051), *p*=0.768 VEP2N75 (n=335): 0.091 (0.059), *p*=0.123 VEP2P100 (n=332): 0.020 (0.059), *p*=0.743 VEP2N150 (n=321): -0.065 (0.060), *p*=0.277 VEP2Amp (n=314): 0.002 (0.052), *p*=0.976 VEP3N75 (n=329): 0.043 (0.060), *p*=0.469 VEP3P100 (n=328): -0.010 (0.060), *p*=0.873 VEP3N150 (n=326): 0.065 (0.060), *p*=0.283	Concurrent blood Pb was significantly associated with decreased interpeak latencies in a neurophysio-logical measure of a visually evoked potential in 6 year old

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				latencies and psychophysical measures of contrast sensitivity (CS) measurements. Visual acuity measurements used as a control for other measurements. Urine Hg also measured.		VEP3Amp (n=319): 0.043 (0.053), *p*=0.417 VEP1:N150-P100 (n=329): -0.081 (0.059), *p*=0.086 **VEP1:P100-N75 (n=336): -0.174 (0.059), *p*=0.002** **VEP1:N150-N75 (n=329): -0.156 (0.058), *p*=0.004** VEP2:N150-P100 (n=321): -0.083 (0.059), *p*=0.080 VEP2:P100-N75 (n=332): -0.048 (0.059), *p*=0.207 VEP2:N150-N75 (n=321): -0.096 (0.059), *p*=0.053 VEP3:N150-P100 (n=325): 0.068 (0.060), *p*=0.129 VEP3:P100-N75 (n=328): -0.042 (0.060), *p*=0.241 VEP3:N150-N75 (n=325): 0.037 (0.060), *p*=0.270 The two results with p < 0.05 remained significant after Bonferoni correction for multiple testing (data not shown) Blood Pb was not significantly associated with psychophysical outcomes. Urine Hg was not associated with neurophysiological measures but was significantly associated with psychophysical outcomes.	children.
Prospective Baghurst (1992) Port Pirie, Australia *Population may overlap with Wigg (1988) and others*	494 7-year old children living in and around the Pb smelting town of Port Pirie, South Australia, followed since birth; re-evaluated at age 7; Year = 1979-1982 (at baseline) % male not stated	7 years (median age: 186 days after 7th birthday)	Means by quartile: (Q1 low - Q4 high) Maternal 6.2, 8.7, 10.6, 14.3 Cord (mean 8.9) 4.3, 7.4, 9.9, 15.0 Lifetime 0-15 months 9.9, 14.3, 18.0, 23.8 Lifetime 0-2 years 11.6, 16.6, 20.5, 27.1 Lifetime 0-3 years 12.2, 17.4, 21.7, 28.2 Lifetime 0-5 years 11.8, 17.0, 21.1, 26.9 Lifetime 0-7 years 10.8, 15.7, 19.7, 24.8	IQ as measured by the Wechsler Intelligence Scale for Children-Revised (WISC-R)	Multiple regression analysis Sex, parents' level of education, maternal age at delivery, parents' smoking status, socioeconomic status, quality of home environment, maternal IQ, birth weight, birth order, feeding method, duration of breast feeding, and whether child's natural parents were living together	Adjusted Multiple regression of log blood Pb and lifetime averages with Full Scale IQ at age 7: *β*(SE) Maternal blood Pb: -1.4 (2.0); p=0.48 Cord blood Pb: 0.60 (1.4); p=0.68 **Blood Pb 0-15 months: -4.0 (2.0); p=0.04** **Blood Pb 0-2 years: -4.6 (2.1); p=0.03** **Blood Pb 0-3 Years: -4.8 (2.3); p=0.04** **Blood Pb 0-4 Years: -4.6 (2.4); p=0.05** Blood Pb 0-7 Years: -3.7 (2.5); p=0.14 Verbal IQ had larger effect sizes and similar significance levels at full scale IQ. Performance IQ was not related to blood Pb at any age Estimated regression coefficients for subscale scores and lifetime average blood Pb 0-3 years: *β*(SE) **Information: -1.45 (0.57), *p* = 0.01** Similarities: -0.90 (0.62), *p* = 0.14 Arithmetic: -0.51(0.63), *p* = 0.42 Vocabulary: -0.44 (0.51), *p* = 0.40 Comprehension: -0.88 (0.54), *p* = 0.10 Picture Completion: -0.15 (0.45), *p* = 0.74 Picture Arrangement: -0.34 (0.60), *p* = 0.56 **Block Design: -1.61 (0.62), *p* = 0.01** Object Assembly: -0.08 (0.50), *p* = 0.86 Coding: -0.22 (0.53), *p* = 0.66	Blood Pb levels sampled from birth to 4 years were significantly associated with lower full scale and verbal IQ, but not performance IQ, at 7 years of age. Average lifetime blood Pb from 0-3 years was significantly associated with the Information and Block Design subscales.

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Prospective Baghurst (1995) Port Pirie, Australia *Population may overlap with Wigg (1988) and others*	494 children (48.2% male) living in and around the Pb smelting town of Port Pirie, South Australia, followed since birth; re-evaluated at age 7; Year = 1979-1982 (at baseline) % male not stated	7-8 years	Maternal: 9.5 Cord: 8.4 6 months: 14.4 2 years: 21.2 (peak) 7 years: 11.6 SD not reported (Pb levels declined from age 2 to 7 with intermediate values included in a figure)	Developmental status assessed at age 7 with the Beery Developmental Test of Visual-Motor Integration (VMI)	Multiple regression models All models included: gender, birth order, months at school, age at testing, maternal IQ, parental smoking, SES and HOME scores. Some models included: Mother's education (maternal, cord, 6 mo), infant feeding style (maternal, cord, 6 mo), duration of breast-feeding (maternal, cord, 6 mo), whether parents live together (cord and 36 mo), father's education (15, 24, 72 and 0-84 mo)	Regression of Visual-Motor Integration Score on Log Blood Pb Concentration: β (SE) Maternal: Simple: -1.80 (0.41); Partial: -0.93 (0.46) Cord: Simple: -0.61 (0.30); Partial: -0.01 (0.33) 6 months: Simple: -1.41 (0.33); Partial: -0.75 0.35) 15 months: Simple: -1.59 (0.33); Partial: -0.83 (0.36) 24 months: Simple: -1.82 (0.38) ; Partial: -0.94 (0.42) 36 months: Simple: -2.10 (0.37); Partial: -1.36 (0.42) 48 months: Simple: -1.84 (0.36) ; Partial:-1.40 (0.39) 60 months: Simple: -1.58 (0.35) ; Partial: -0.81 (0.39) 72 months: Simple: -1.81 (0.35) ; Partial:-0.83 (0.41) 84 months: Simple: -1.85 (0.33) ; Partial:-1.30 (0.37) 0-84 months: Simple: -2.39 (0.51) ; Partial: -1.47 (0.60) *Statistical significance of these results not reported.* For an increase in lifetime average blood Pb from 10 to 30 µg/dL the significant estimated deficit in children's visual-motor performance was **1.6 points (95% CI = 0.3-2.9**)	Pre and postnatal blood Pb levels were associated with lower visual-motor performance at age 7.
Prospective Bandeen-Roche (2009) Baltimore, MD, USA *Population may overlap with Shih (2006) and others*	964 adults from the Baltimore Memory Study, aged 50 – 70 years, residing in Baltimore for at least 5 years. Year not stated Male= 34.3%	59.3 (6.0) years at baseline	Tibia Pb: 18.8 (11.6) µg/g at first follow-up 18.5 (11.6) µg/g at second follow-up Exposure measured at first and second follow-up visits	Cognitive function assessed by a 90-minute battery of 20 standardized tests covering 6 cognitive domains: *language* (Boston naming test, letter fluency, category fluency); *processing speed* (inverse or reaction time); e*ye-hand coordination* (Purdue pegboard hands and trail-making test A); *executive functioning* (Purdue pegboard assembly Stroop C minus A form, trail making test B minus A); *Verbal memory and learning* (Rey auditory verbal learning test); *Visual memory* (Rey	Marginal longitudinal linear regression, Q-normal plots, regression models, Age, sex, neurobehavioral testing technician, race/ethnicity, educational attainment, household wealth Adjusted for age, sex, interviewer, SES, and race (if applicable)	Tests of changing effect hypothesis: Eye-hand coordination (p=0.0035) **low-level Pb: β = -0.036 (-0.075, 0.004)** **high-level Pb: β = 0.020 (-0.027, 0.068)** **p=0.0035** An African-Americans only analysis retained a significant association with eye-hand coordination (p=0.0062), but whites were not significantly associated with any domain. Race and SES adjusted Domain Score Difference per 12.7 µg/g tibia Pb mean (95% CI): Baseline eye-hand coordination = -0.005 (-0.052, 0.042) Yearly difference amplification = -0.019 (-0.031, -0.007) No cognitive function domains were significantly associated in African Americans before or after adjusting for SES, or in the total sample after adjusting for race and SES. In White subjects only, adjusted domain score difference with a 12.7 (IQR) of tibia Pb: Mean (95% CI) Language: -0.0241 (-0.0764, 0.0281), p = 0.33 Processing Speed: -0.0241 (-0.1162, 0.068), p = 0.83	Tibia Pb was significantly associated with decreased hand eye coordination in adults, particularly in African-Americans, while other cognitive function domains were only significantly associated in white subjects.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				complex figure)		**Eye-hand coordination: -0.0635 (-0.1183, -0.0087),** p = 0.071 **Executive functioning: -0.0635 (-0.1158, -0.0112),** p = 0.053 **Verbal memory and learning**: -0.0762 (-0.1534, 0.001), ***p* = 0.034** Visual memory: -0.0648 (-0.1544, 0.0248), p = 0.31	
Prospective Bellinger (1984) Boston, MA, USA *Population may overlap with Bellinger (1986) and others*	249 middle and upper-middle class children delivered at the Brigham and Women's Hospital from the Boston Lead Study of child development; Year= born between 1979-1981 % male not stated	6 months	Cord (mean) 6.6 (3.2) Cord blood Pb by categories (mean) Low: 1.8 Mid: 6.5 High: 14.6	Development as assessed by the Mental Development Index (MDI) and Psychomotor Development Index (PDI) of the Bayley Scales of Infant Development	Multiple regression analyses, Spearman rank-order correlation Length of gestation, total HOME score PDI: additionally adjusted for presence of a problem being followed by an infant's pediatrician at 6 months	<u>Adjusted Regression of MDI and cord blood Pb</u> -2.891 (SE 0.210), p = 0.0019 95% CI for mean decrease in MDI score: -1.1, -4.7 <u>Correlation of cord blood Pb and MDI</u>: -0.11, p = 0.10 <u>Scores on item clusters from MDI Bayley Scales of Infant Development by cord blood Pb</u>: Low, mid, high, p-value Gross Motor: 8.3, 8.1, 8.2; p = 0.215 **Fine Motor: 9.6, 9.7, 9.2; *p* = 0.022** **Social Responsiveness: 6.9, 6.8, 6.7; *p* = 0.014** Goal Directedness: 3.2, 3.3, 3.1; p = 0.188 **Visually Directed Reaching: 8.2, 8.1, 7.9; *p* = 0.016** Secondary Circular Reactions: 1.8, 1.9, 1.8; p = 0.928 Object Permanence: 2.4, 2.4, 2.4; p = 0.794 Vocalization/Language: 4.0, 3.9, 3.9; p = 0.276 Log of 6 month blood Pb was not significantly associated with MDI PDI measures were not significantly associated with cord blood Pb or log 6 month blood Pb.	Cord blood Pb was significantly associated with lower scores on the MDI, but not the PDI, at 6 months. Concurrent blood Pb was not associated with MDI or PDI scores at 6 months.
Prospective Bellinger (1986) Boston, MA, USA *Population may overlap with Bellinger (1984) and others*	249 middle and upper-middle class children delivered at the Brigham and Women's Hospital from the Boston Lead Study of child development; Year= born between 1979-1981 % male not stated	6, 12, 18, 24 months	Cord: 6.6 (3.2) Categorized into: Low <3 Mid 6-7; High >=10 6 months: 6.2 (7.1) Range 0-48.6 12 months: 7.7 (6.5) Range 0-30.6	Development as assessed by the Mental Development Index (MDI) of the Bayley Scales of Infant Development at 6 and 12 months	Simple bivariate regression without adjustment for confounding Stepwise/simultaneous multivariate regression Length of gestation, and total HOME score	<u>Bivariate associations between MDI and Pb</u>: est. (SE) 6 mon. MDI, Cord blood Pb: -1.49 (1.01), p = 0.14 6 mon. MDI, 6 mon. blood Pb: 0.65 (0.94), p = 0.49 12 mon. MDI, Cord blood Pb: -2.04 (1.11), p = 0.07 12 mon. MDI, 6 mon. blood Pb: -0.74 (1.04), p = 0.48 12 mon. MDI, 12 mon. blood Pb: -0.41 (1.08), p = 0.71 <u>Adjusted multivariate regression for MDI scores and Cord blood Pb:</u> β (95% CI) **6 mon. MDI: -2.89 (-1.09, -4.69); p=0.0019** **12 mon MDI: -3.63 (-1.43, -5.83); p=0.0015** <u>Adjusted multivariate regression MDI Scores at 12 months and Cord blood Pb</u>: mean (SD) **Fine motor: p=0.0004** **Low: 4.3 (1.6); Mid: 4.3 (1.6); High: 3.3 (1.7);** **Imitation: p=0.011**	Cord blood Pb was significantly associated with lower MDI scores at 6 and 12 months, but postnatal blood Pb was not associated with MDI scores.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Low: 4.2 (1.0); Mid: 4.1 (1.0); High: 3.7 (1.2); Object permanence: p=0.74 Low: 3.8 (0.5); Mid: 3.8 (1.0); High: 3.9 (0.4); **Language: p=0.018** **Low: 4.6 (1.5); Mid: 4.9 (1.8); High: 4.0 (1.2);** Spatial: p=0.064 Low: 0.8 (0.8); Mid: 0.6 (0.8); High: 0.6 (0.8); Goal directed: p=0.25 Low: 2.4 (1.2); Mid: 2.3 (1.1); High: 2.3 (1.0);	
Prospective Bellinger (1987) Boston, MA, USA *Population may overlap with Bellinger (1984) and others*	249 middle and upper-middle class children delivered at the Brigham and Women's Hospital from the Boston Lead Study of child development; Year= born between 1979-1981 Male=59.3%	6, 12, 18, 24 months	Cord: 6.6 (3.2) Categorized into: Low, <3; Medium, 6-7; High, >=10	Development as assessed by the Mental Development Index (MDI) of the Bayley Scales of Infant Development	Least Squares Regression Mother's age, race, IQ, education, years of smoking, and 3rd trimester alcoholic drinks per week; mean family social class during the study, quality of the care-giving environment, gender, birth weight, gestational age, and birth order	<u>Infants' adjusted MDI Scores by Cord-Blood Pb Group</u>: 6 months (N=201) p=0.095 Low: 110.2 (1.3); Med: 108.0 (1.3); High: 105.9 (1.4) **12 months (N=199) p=0.020** **Low: 114.7 (1.6); Med: 114.4 (1.5); High: 108.9 (1.6)** **18 months (N=187) p=0.049** **Low: 116.2 (1.9); Med: 114.8 (1.9); High: 109.5 (2.0)** **24 months (N=182) p=0.006** **Low: 118.9 (1.8); Med: 117.8 (1.7); High: 111.1 (1.8)** Estimated difference between: Low and high groups **4.8 points (95% C.I. 2.3, 7.3)** Medium and high groups **3.8 (95% C.I. 1.3, 6.3).**	Cord blood Pb level was significantly associated with lower MDI scores at 12, 18, and 24 months, while postnatal blood Pb was not significantly associated with MDI scores.
Prospective Bellinger (1990) Boston, MA, USA *Population may overlap with Bellinger (1984) and others*	170 middle and upper-middle class children delivered at the Brigham and Women's Hospital from the Boston Lead Study of child development; Year= born between 1979-1980 % male not stated	Blood measured from birth through 57 months Median age at final assessment: 57.8 months	Exposure measured at birth (umbilical cord), 6, 12, 18, 24, and 57 months Categorized into: Low < 3µg/dL Medium 3-10µg/dL High ≥ 10µg/dL *No mean, SD, range, or number in each category reported here*	Change in cognitive performance (Δz): an index of a child's developmental trajectory between 24 and 57 months. Calculated as the difference in z-scores (Δz) from measures: cognitive function as assessed by the Mental Development Index (MDI) scores from the Bayley Scales of Infant Development at 24 months and by the General Cognitive Index (GCI) score from the McCarthy	Multiple regression analysis; stratified analyses Adjusted for MDI at 24 months, HOME score at 57 months, social class, maternal IQ, maternal age, gender, and ethnicity	<u>Adjusted regression coefficients for change in cognitive performance (Δz) and blood Pb:</u> β(SE) **Cord blood Pb: 0.03 (0.01); p=0.016** 6 months blood Pb: 0.00 (0.07); p=0.96 12 months blood Pb: -0.08 (0.07); p=0.23 **18 months blood Pb: -0.21 (0.08); p=0.007** **24 months blood Pb: -0.22 (0.08); p=0.005** **57 months blood Pb: -0.23 (0.10); p=0.028** <u>Regression coefficients β(SE) for predictors of Δz in each cord blood Pb stratum</u>: Low cord blood (< 3µg/dL) Cord blood Pb: 0.04 (0.11); p=0.72 6 months blood Pb: -0.01 (0.10); p=0.94 12 months blood Pb: -0.18 (0.09); p=0.063 18 months blood Pb:-0.13 (0.09); p=0.16 24 months blood Pb: -0.16 (0.08); p=0.057 57 months blood Pb:-0.16 (0.14); p=0.26 Medium cord blood (3-10µg/dL) Cord blood Pb: 0.10 (0.29); p=0.74 6 months blood Pb: 0.02 (0.12); p=0.88 12 months blood Pb: 0.03 (0.13); p=0.84	Postnatal blood Pb levels were significantly associated with greater declines in scores on cognitive tests between age 2 and age 5.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				Scales of Children's Abilities at 57 months		**18 months blood Pb:-0.34 (0.150; p=0.028** 24 months blood Pb: -0.31 (0.16); p=0.065 57 months blood Pb: -0.14 (0.22); p=0.52 High cord blood (≥ 10µg/dL) Cord blood Pb: 0.07 (0.04); p=0.07 6 months blood Pb: 0.01 (0.13); p=0.95 12 months blood Pb: -0.18 (0.14); p=0.20 18 months blood Pb:-0.16 (0.16); p=0.33 24 months blood Pb: -0.28 (0.16); p=0.079 **57 months blood Pb: -0.46 (0.18); p=0.013**	
Prospective Bellinger (1991) Boston, MA, USA *Population may overlap with Bellinger (1984) and others*	170 middle and upper-middle class children delivered at the Brigham and Women's Hospital from the Boston Lead Study of child development; Year=1979-1981 Male=51.2%	Children enrolled at birth Cognitive assessment at 57 months Median age (days): Session 1: 1777 Session 2: 1796	Cord: 6.8 (6.3) 6 months: 6.8 (7.3) 12 months: 7.8 (6.4) 18 months: 8.0 (5.7) 24 months: 7.0 (6.6) 57 months: 6.4 (4.1) 57 months tooth Pb: 2.8 (1.7) µg/g *abstract states that 24 month mean is 6.8 (6.3)µg/dL	General Cognitive Index (GCI) at 57 months; The McCarthy Scales of Children's Abilities, five subscale scores: verbal, perceptual-performance, quantitative, memory, and motor	Multiple regression Family social class, maternal IQ, marital status, preschool attendance, HOME total, hours per week of "out of home" care, number of family residence changes, recent medication use, number of adults in household, gender, race, birth weight, and birth order	<u>Adjusted mean change in GCI at 57 months for each natural log increase in Pb at one age</u>: β(95% CI), *P* value 6 month Pb: 0.28 (-2.3, 2.8); p=0.83 12 month Pb: -1.43 (-3.9, 1.0); p=0.25 18 month Pb: -1.62 (-4.3, 1.1); p=0.25 **24 months Pb: -2.95 (-5.7, -0.2); p=0.040** 57 month Pb: -2.28 (-6.0, 1.4); p=0.23 Dentine Pb: -2.51 (-10.2, 5.2); p=0.52 <u>Adjusted mean change in GCI at 57 months for each natural log increase in Pb level over age spans</u>: β(SE), *P* value Birth-57mo: -2.76 (2.41), *P* = 0.25 6-57mo: -2.33 (2.22), *P* = 0.30 12-57mo: - 2.17 (1.98), *P* = 0.28 18-57mo: - 2.94 (1.19), *P* = 0.13 24-57mo: - 2.80 (1.59), *P* = 0.08 <u>Adjusted mean change in 57 month Subscale Scores for each natural log increase in blood Pb at 24 or 57 months</u>: β(SE), *P* value Verbal 24 months: -0.41 (1.04); p=0.69 57 months: -1.06 (1.38); p=0.44 **Perceptual-Performance** **24 months:-2.58 (0.88); p=0.004** **57 months:-2.33 (1.13); p=0.042** Quantitative 24 months:-1.45 (0.85); p=0.09 57 months:0.13 (1.13); p=0.91 Memory 24 months:-0.66 (0.94); p=0.49 57 months: 0.49 (1.25); p=0.70 Motor 24 months:-0.90 (0.92); p=0.33 57 months:-1.89 (1.15); p=0.10 Cord blood Pb levels were not significantly associated	Blood Pb at 24 months was significantly associated with lower GCI scores at age 57 months. Blood Pb at 24 and 57 months were significantly associated with decreased perceptual performance at age 57 months.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						with GCI scores at 57 months of age unless concurrent Pb levels were above 10µg/dL	
Prospective Bellinger (1992) Boston, MA, USA *Population may overlap with Bellinger (1984) and others*	148 middle and upper-middle class children delivered at the Brigham and Women's Hospital from the Boston Lead Study of child development; Year= born between 1979-1980 Male=50.7%	10 years	6 months: 6.7 (7.0) 12 months:7.7 (6.5) 18 months: 7.8 (5.7) 24 months: 6.5 (4.9) 57 months: 6.3 (3.8) 10 years: 2.9 (2.4) Cord blood Pb ≥10µg/dL: 28.6%	Wechsler Intelligence Scale for Children-Revised (WISC-R) and the Kaufman Test of Educational Achievement (K-TEA)	Multiple regression Adjustments include HOME at age 10 and 57 months, family stress, child stress, maternal age, race, birth weight, maternal IQ, SES, sex, birth order, and marital status number of residence changes prior to 57 months, family balance, and parent's sense of competence,	<u>Adjusted regression of WISC-R and K-TEA at age 10 and a 10µg/dL increase in blood Pb at 24 months</u>: coefficient (SE), *P* **Full-Scale IQ: -0.58 (0.21), *P* = 0.007** **Verbal IQ: -0.63 (0.22), *P* = 0.004** Performance IQ: -0.396 (0.23), *P* = 0.091 **K-TEA Battery Composite: -0.89 (0.24), *P* = 0.0003** **Mathematics Composite: -0.91 (0.29), *P* = 0.002** Reading Composite: -0.38 (0.21), *P* = 0.078 **Spelling: -0.97 (0.28), *P* = 0.0008** Blood Pb at birth (Cord: low and med vs. high), 6, 12, 18, and 57 months, and 10 years were not associated with any of the cognitive test scores (all p > 0.05).	Blood Pb at 24 months was significantly associated with lower cognitive test scores at age 10. Cord blood Pb and 5 postnatal blood Pb measures were not significantly associated with any of the cognitive measures.
Prospective Bellinger (1994b) Boston, MA, USA *Population may overlap with Leviton (1993)*	1,782 children born at the Lying-In Division of the Boston Hospital for Women; Year = 1979-1980 Male=50%	8 years	Cord: 6.8 (3.1) Deciduous tooth dentin Pb (µg/g): 3.4 (2.4)	Children's behavior measured using the Teacher Report Form (TRF) of the Child Behavior Profile	Multiple logistic regression Adjustments include pre-pregnant weight, birth weight, race, cesarean section, parental education, sex, parents living together in child's first year, aspirin use in week before delivery, urinary tract infection during pregnancy, current medication use by child, mother smoking during pregnancy, mother married at time of delivery, mother on public assistance at time of delivery, prenatal care begun after first trimester, colic, and sibship size	<u>Adjusted regression for summary T scores associated with each log unit increase in Pb</u>: estimate (95% CI), *p* Cord blood Pb: Total problem behaviors: -0.02 (-1.21, 1.17); *p*=0.98 Internalizing: -0.27 (-1.30, 0.75); *p*=0.60 Externalizing: 0.08 (-0.92, 1.09); *p*=0.87 **Tooth Pb:** **Total problem behaviors: 2.06 (0.93, 3.18) *p*=0.0003** **Internalizing: 1.61 (0.62, 2.60); *p*=0.002** **Externalizing: 1.57 (3.64, 2.50); *p*=0.001** <u>Adjusted Odds Ratio for extreme summary scores associated with a log unit increase in Pb</u>: OR (95% CI) Cord blood Pb: Total problem behaviors: 0.94 (0.63, 1.42), *p*=0.78 Internalizing: 1.06 (0.74, 1.53), *p*=0.74 Externalizing: 0.95 (0.63, 1.43), *p*=0.79 Tooth Pb: Total problem behaviors: 1.42 (0.95, 2.13), *p*=0.092 Internalizing: 1.39 (0.98, 1.97), *p*=0.064 Externalizing: 1.41 (0.94, 2.12), *p*=0.099	Pb levels in primary teeth was significantly associated with internalizing, externalizing and total problem behaviors, but cord blood Pb was not associated. An association between tooth Pb and an extreme problem behavior score was not statistically significant.
Prospective Bellinger (1994a)	79 subjects who were a portion of a	19-20 years	Blood Pb: ≤5	Neuropsychological tests for Children: 1)	Multiple regression analyses	Association with attention factors: *F* (d.f.), *p*-value or coefficient (SE), *p* for individual task results	Dentin Pb levels were

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Boston, MA, USA	cohort of adolescents recruited as first and second graders; Year=dentine collected 1975-1978, blood and bone Pb collected 1989-1990 Male= 43%		Dentin Pb: 13.7 (11.2) µg/g Tibia Pb: 5.4 µg/g Patella Pb: 9.2 µg/g	Encode factor: Digit span subtest of the Wechsler Intelligence Scale for Adults-revised and arithmetic subtest of the Wechsler Intelligence Scale for Adults-revised; 2) Focus-execute factor: Talland Letter Cancellation test, Stroop Color-Word interference Test, digit-symbol subtest of the Wechsler Intelligence Scale for Adults-revised, and Trail-making Test; 3) Sustain factor: A visual Continuous performance Test (CPT); 4) Shift factor: number of errors on the Wisconsin Card Sorting Test, ALA-D isozyme phenotype	Parent IQ, mother's age at the time of child's birth, maternal education, family social class, sex, birth order, current cigarette smoker, current illicit drug use, and current alcohol use	Dentin Pb levels: **Focus-execute factor: 3.15 (4, 53), *p*=0.022** **Shift factor: 8.82 (1, 57) *p*=0.004** Encode factor: 1.26 (2, 56), *p*=0.29 Sustain factor: 1.38 (3, 47), *p*=0.26 Tibia Pb levels: **Focus-execute factor: *p*=0.037** Shift factor: not significant Encode factor: not significant Sustain factor: not significant Patella Pb levels: No significant association with any of the attention factors 5 individuals with the 1-2 ALA-D phenotype (all others 1-1) had mean dentin Pb of 8.0 ppm (vs. 14.1), tibia Pb levels below 6 µg/g (vs. 19.9 % in 1-1), yet all had patella Pb levels above 6µg/g (vs. 43% in 1-1). After adjusting for dentin Pb, the 5 subjects with the 1-2 phenotype had more optimal scores on almost every endpoint, but p-values are not reported due to the limited sample size.	significantly associated with lower scores on two of four attention factors: focus-execute and shift; tibia Pb levels were significantly associated with lower focus-execute factor scores; but patella Pb levels were not associated with any attention factors. A rare ALA-D isozyme phenotype may modify Pb stores and the relationship between tooth Pb and attention.
Cross-sectional Bellinger (2005) Chennai, India	54 children aged 4 to 14 from a rural primary school; Year not stated Male=74.2%	6.7 (2.1) years	11.1 (5.6) µg/dL	Neurobehavioral function: the Binet-Kamath IQ test, the Wide Range Assessment of Visual Motor Activity (WRAVMA), Connor's Behavioral Rating Scale (both parents and teachers).	Linear regression Maternal age, father and mother living together, parents' education, parents' occupation, family income, child's gender, age, class (grade), early feeding method, and birth order.	Regression coefficient for IQ and concurrent blood Pb: Unadjusted: -0.62 (95% CI -1.84, 0.59), *p* = 0.31 Adj. for maternal age: -1.10 (-2.63, 0.44), *p* = 0.16 Adj. for paternal educ.: -0.47 (-1.70, 0.76), *p* = 0.21 [other adjustments were between the 2 above] After adjustment for all covariates: Median value= -0.76 Mean (SD) IQ in highest quartile: 95.6 (12.3) Mean (SD) IQ in lowest quartile: 102.0 (22.5) Regression coefficient for WRAVMA and concurrent blood Pb: Unadjusted: -0.44 (95% CI -1.76, 0.88), *p* = 0.51 [Adjustments ranged between -1.18 (-2.7, 0.34), p=0.12 and -0.32 (-1.64, 0.99), *p* = 0.62] After adjustment for all covariates: Median value= -0.88 Behavior Ratings were not associated with blood Pb.	Concurrent blood Pb was not significantly associated with IQ or WRAVMA composite scores in children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Cross-sectional Bouchard (2009) USA *Population may overlap with Braun (2006)*	1987 adults from NHANES 1999-2004; Year= 1999-2004 Male= 44%	Range = 20 – 39 years	1.61 (1.72) µg/dL Range = 0.3 – 37.3 µg/dL Current blood Pb level measures	Psychiatric Outcomes were assessed using three diagnostic modules of WHO's Composite International Diagnostic Interview: Major Depressive Disorder, Panic Disorder and Generalized Anxiety Disorder.	Linear trend analysis and logistic regression models using $\log_{10}$ transformed blood Pb values. Sex, age, race/ethnicity, education status, poverty to income ratio,	Logistic Regression Analyses by blood Pb quintile: **Major Depressive Disorder (p=0.05 for trend)** 1st (≤7 µg/dL), OR = reference 2nd (0.71-1.0 µg/dL), OR =1.39 (0.71, 2.72) 3rd (1.01-1.4 µg/dL), OR =1.28 (0.69, 2.38) 4th (1.41-2.1 µg/dL), OR =1.41 (0.76, 2.60) **5th (≥2.11 µg/dL), OR =2.32 (1.13, 4.75)** **Panic Disorder (p=0.02 for trend)** 1st (≤7 µg/dL), OR = reference 2nd (0.71-1.0 µg/dL), OR=2.88 (0.72, 11.49) 3rd (1.01-1.4 µg/dL), OR =1.80 (0.44, 7.44) 4th (1.41-2.1 µg/dL), OR =3.13 (0.78, 12.57) **5th (≥2.11 µg/dL), OR = 4.94 (1.32, 18.48)** Generalized Anxiety Disorder (p=0.78 for trend) 1st (≤7 µg/dL), OR = reference 2nd (0.71-1.0 µg/dL), OR =1.26 (0.47, 3.36) 3rd (1.01-1.4 µg/dL), OR =2.25 (0.75, 6.70) 4th (1.41-2.1 µg/dL), OR =2.16 (0.76, 6.09) 5th (≥2.11 µg/dL), OR =1.53 (0.39, 5.96)	Blood Pb was significantly associated with major depression disorder and panic disorder but not generalized anxiety disorder
Prospective Boucher (2009) Quebec, Canada *Population may overlap with Despres (2005)*	104 Inuit children were assessed at 5 years and 201 children were assessed at 11 years from whom umbilical cord blood samples had been obtained in the Cord Blood Monitoring Program(80 children were assessed at both 5 and 11 years) Years=1993-1998 Male= 41% at 5 yrs Male= 45% at 11 yrs	5.4 years (range = 4.8 – 6.2 years) 11.3 years (range = 10.2 – 12.9 years)	Cord blood levels in children assessed at 5 years: 4.9 µg/dL (range = 0.8 – 27.1 µg/dL) Cord blood levels in children assessed at 11 years: 4.8 µg/dL (range = 0.8 – 20.9 µg/dL)	A visual oddball paradigm was used to elicit the P3b wave at 5 years, and an auditory oddball paradigm was used to elicit the P3b wave at 11 years.	Pearson correlations and multiple regression analyses. Maternal non-verbal intelligence, breastfeeding status, Hg levels, hemoglobin, PCB-153 levels, and age at testing, socio-economic status.	Cord blood Pb and P3b parameters: P3b Amplitude at 5 years **Pearson r = -0.38; p≤0.05** **Standardized β = -0.38; p≤0.05** P3b Amplitude at 11 years Pearson *r*= -0.06; p=NS Standardized β= -0.04; p=NS Blood Pb at 5 years and P3b parameters: P3b Latency at 5 years Pearson r =-0.25; p=NS Standardized β = 0.08; p=NS P3b Latency at 11 years Pearson r= 0.07; p=NS Standardized β= 0.00; p=NS	Cord blood Pb was significantly associated with a decrease in P3b amplitude at age 5 years but not at 11 years or P3b latency
Cross-sectional Braun (2006) USA *Population may overlap with Bouchard (2009)*	4,704 participants from NHANES 1999-2002 Years=1999-2002 Male=48%	mean not reported Range = 4 – 15 years 4-6, n=1018 7-9, n=1003	mean not reported 3rd quintile: 1.1-1.3	ADHD: Parent reported previous diagnosis of ADHD use of stimulant medication, prenatal and postnatal tobacco smoke	Logistic regression analysis, Chi-square, multivariable main effects model. Child's age, sex, race, prenatal ETS exposure,	Logistic regression analysis, adjOR (95% CI) for parent-reported ADHD with prescription stimulant use Blood Pb quintiles (µg/dL): 1st quintile (ND-0.70): referent 2nd quintile (0.8-1.0): 1.1 (0.4, 3.4); p=0.804 3rd quintile (1.1-1.3): 2.1 (0.7, 6.8); p=0.195 4th quintile (1.4-2.0): 2.7 (0.9, 8.4); p=0.086	Blood Pb was significantly associated with a parent-reported diagnosis of ADHD in

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
		10-12, n=1182 13-15, n=1501		exposure	postnatal ETS exposure, blood Pb levels, preschool or child care attendance, health insurance coverage, and ferritin levels	**5th quartile (>2): 4.1 (1.2, 14.0); p=0.026** Prenatal tobacco smoke exposure No – referent **Yes adjOR = 2.5(1.2,5.2); p=0.020** Postnatal tobacco smoke – smoker in home No – referent Yes adjOR = 0.6(0.3,1.3); p=0.224 Population attributable fraction for parent-reported ADHD and stimulant medication: Blood Pb >2.0 µg/dL: 27.9% exposed; OR=4.1; 21.1% attributable (95% CI 4.7-25.9) = 290,000 excess cases Prenatal tobacco: 30.7% exposed; OR=2.5; 18.4% attributable (95% CI 5.1-24.8) = 270,000 excess cases Blood Pb >2.0 µg/dL AND prenatal tobacco: 46.2% exposed; OR=3.3; 32.2% attributable (95% CI 4.2-41.3) = 480,000 excess cases	children aged 4-15.
Cross-sectional Braun (2008) USA *Population may overlap with Braun (2006)*	3,081 children ages 8-15 years from NHANES; Year=2001-2004; Male=49.2%	8-15 years	mean not reported 1st quartile (22.8%): 0.2-0.7 2nd quartile (23.4%): 0.8-1.0 3rd quartile (21.8%): 1.1-1.4 4th quartile (33%): 1.5-10.0	Conduct disorder (CD) measured by Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV)	Logistic regression Child's age in years, poverty-to-income ratio, maternal age at child's birth, child's sex, child's race, prenatal tobacco smoke exposure, cotinine levels, and blood Pb levels	Adjusted odds ratio for meeting DSM-IV CD criteria by blood Pb levels (quartiles): 1st (0.2-0.7 µg/dL): referent **2nd (0.8-1.0 µg/dL) Adj.OR= 7.24 (1.06-49.47)** **3rd (1.1-1.4 µg/dL) Adj.OR= 12.37 (2.37-64.56)** **4th (1.5-10.0 µg/dL) Adj.OR= 8.64 (1.87-40.04)** Poisson regression analysis for CD symptom count in past year by blood Pb levels (quartiles): 1st (0.2-0.7 µg/dL): referent **2nd (0.8-1.0 µg/dL) Adj.SR=1.55 (1.09, 2.22)** **3rd (1.1-1.4 µg/dL) Adj.SR=1.50 (1.04, 2.17)** **4th (1.5-10.0 µg/dL) Adj.SR (1.23, 2.43)** OR for meeting DSM-IV CD criteria and for CD symptom count in the past year was also significant for prenatal tobacco exposure and serum cotinine in the 4th and 5th quintiles.	Blood Pb was significantly associated with conduct disorder in children aged 8-15.
Prospective Brubaker (2009) Cincinnati, OH, USA *Population may overlap with Dietrich (1987) and others*	91 children of participants of the Cincinnati Lead Study (CLS) were followed up as adults Year=1979-1984 Male=43%	22.9 (1.5) years Range = 20.0 – 26.1 years	12.9 (6.2) µg/dL Range = 4.8 – 37.3 µg/dL Exposure measured 23 times during first 6.5 years.	Adult white matter architecture was evaluated using Diffusion Tensor Imaging (DTI).	Multiple regression analysis using a general linear model; simple voxel-wise regressions. Maternal prenatal tobacco and alcohol use, maternal IQ, gestational age, adult marijuana use, age at imaging,	Statistics not reported; authors state the following conclusions: The fractional anisotropy (FA) map Inverse association between FA and blood Pb levels in diffusely scattered white matter regions. The mean diffusivity (MD) map Inverse (corpus callosum), and direct (superior corona radiate) correlations with blood Pb levels. The axial diffusivity (AD) map Inverse association between AD values and blood Pb levels within the anterior and superior corona radiata. The radial diffusivity (RD) map	Blood Pb in children under 6 years of age was associated with changes in white matter microstructure as quantified with diffusivity changes suggestive of altered

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Inverse (corpus callosum and internal capsule) and direct (superior corona radiate) correlations with blood Pb levels.	myelination and axonal integrity.
Prospective Burns (1999) Port Pirie, Australia *Population may overlap with Wigg (1988) and others*	322 children (49% male) living in and around the Pb smelting town of Port Pirie, South Australia, followed since birth; re-evaluated at 11-13 yrs of age. Year = 1979-1982 (at baseline)	11-13 years	Lifetime average (geom mean and 95%CI): Boys 14.3 (13.5-15.1) Girls 13.9 (13.2-14.6) Cord blood in this subset: 8.1µg/dL Blood levels at other ages reported in other papers on this cohort. All postnatal exposure measures were qualitatively similar to those reported for lifetime average exposures (data not shown).	Behavior: parents (mothers) completed the Achenbach Child Behavior Checklist and the General Health Questionnaire to assess the parent's psychological adjustment. Family adjustment assessed with the general functioning scale of the McMaster Family Assessment Device. Wechsler Intelligence Scale for Children-Revised (WISC-R) was used to assess each child's intelligence	Multiple linear regression stratified by gender, and multiple logistic regression with a binary outcome variable using the median behavior score Adjusted for maternal age, smoking during pregnancy, birth weight, type of feeding, length of breastfeeding, maternal education, maternal IQ, father's education, maternal psychopathology, birth order, family functioning, father's occupation, parents' smoking habits, marital status, HOME environment, and child's IQ.	Mean behavior problem scores stratified by gender and blood Pb level (µg/dL): ≤15 (SD); >15 (SD); *p* - value **Total, boys: 21.1 (1.9); 28.1 (2.1); *p* < 0.008** **Total, girls: 18.0 (1.7); 29.7 (2.3); *p* < 0.008** Internalizing, boys: 6.4 (0.6); 7.1 (0.7); *p* = 0.45 **Internalizing, girls: 6.1 (0.7); 9.0 (0.8); *p* < 0.008** **Externalizing, boys: 7.4 (0.8); 11.4 (0.8); *p* < 0.008** **Externalizing, girls: 5.8 (0.6); 10.4 (0.8); *p* < 0.008** Change in behavior problem scores from an increase in lifetime blood Pb from 10 to 30µg/dL (at age 11-13): adjusted estimate (95% CI); OR (95% CI) Boys (n=159) **Total problems: 5.2 (0.4, 10.1); 3.2 (1.4, 6.6)** Internalizing problems: 0.8 (-0.9, 2.4); 1.2 (0.6, 2.2) Externalizing problems: **3.5 (1.6, 5.4);** 1.7 (0.8, 3.3) Withdrawn: 0.1 (-0.4, 0.7); 1.5 (0.7, 3.1) Somatic complaints: -0.1 (-0.7, 0.4); 0.8 (0.3, 1.6) Anxious/depressed: 0.8 (-0.2, 1.8); 1.9 (0.9, 4.0) Social problems: 0.4 (-0.2, 1.1); 1.7 (0.8, 3.0) Thought problems: 0.0 (-0.2, 0.3); 1.8 (0.8, 4.0) Attention problems: 0.3 (-0.6, 1.3); 1.2 (0.6, 2.3) **Delinquent behavior: 0.9 (0.3, 1.4); 2.8 (1.4, 5.8)** **Aggressive behavior: 2.7 (1.3, 4.1); 1.9 (1.0, 4.3)** Girls (n=163) **Total problems: 6.2 (1.3, 11.1); 2.8 (1.0, 6.8)** **Internalizing problems: 2.1 (0.0, 4.2); 3.8 (1.4, 11.0)** Externalizing problems: 1.8 (-0.1, 3.7); 2.0 (0.8, 4.6) **Withdrawn: 0.6 (0.0, 1.1); 2.6 (1.0, 6.5)** Somatic complaints: 0.3 (-0.4, 0.9); 1.5 (0.6, 3.3) **Anxious/depressed: 1.3 (0.1, 2.5); 3.1 (1.2, 7.9)** Social problems: 0.3 (-0.3, 0.8); **3.3 (1.2, 9.3)** Thought problems: **0.3 (0.1, 0.5);** insufficient data Attention problems: **1.1 (0.3, 1.8);** 2.0 (0.8, 4.9) Delinquent behavior: 0.2 (-0.1, 0.6); **2.3 (1.0, 5.7)** Aggressive behavior: **1.6 (0.0, 3.2);** 1.9 (0.8, 4.5)	Lifetime average blood Pb in 11-13 year olds was significantly associated with increased total problem behavior scores, with boys having more externalizing behaviors and girls more internalizing behaviors.
Cross-sectional Caffo (2008) DE and NJ, USA	513 former organolead (tetraethyl Pb from 1923-1991; tetramethyl Pb from 1960 to 1983)	60.39 (7.93) in 2001-2003 Range 34.7-78.3	Mean peak tibia Pb: 23.99 (18.46) mg/g Mean time since occupational Pb exposure: 18.01,	Brain volumes were assessed using MRI images. Neurobehavioral and cognitive ability were assessed using: the	A novel statistical strategy was developed by condensing the unmanageable multivariate images with targeted, simpler,	Point estimates (95% CIs) for the association of peak tibia Pb with cognitive domain scores for every µg/g increase in peak tibia Pb: Visuo-construction Gray matter = -3.40 (-8.86, 1.88) White matter = -4.24 (-9.54, 1.06)	Cumulative tibia Pb dose was significantly associated with lower executive

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	manufacturing workers. Years=1994-1997 and 2001-2003 Male=100%		Range 1.5-48.3 years	vocabulary subtest from the Wechsler Adult Intelligence Scale–Revised (WAIS-R); the Rey Auditory Verbal Learning Test (RAVLT); the symbol digit paired associate learning test; the Rey-Osterrieth complex figure, delayed score; the Stroop test; the University of Pennsylvania Smell Identification Test (UPSIT); the finger tapping task; the Purdue pegboard; the Center for Epidemiologic Studies–Depression Scale (CES-D); and the Symptom CheckList-90 (SCL-90).	composite summaries. Adjusted for age, visit number, apolipoprotein E *ε4* allele, Pb exposure duration, education, testing technician, years since last exposure, smoking and alcohol drinking.	Verbal Memory and Learning Gray matter = -2.77 (-6.89, 1.36) White matter = -2.75 (-6.86, 1.35) Visual Memory Gray matter = -1.19 (-5.83, 3.44) White matter = -1.42 (-6.04, 3.19) Executive Function **Gray matter = -5.00 (-8.57, -1.42)** **White matter = -3.79 (-7.40, -0.18)** Eye-hand coordination Gray matter = -3.95 (-8.07, 0.17) White matter = -3.63 (-7.71, 0.45) Processing Speed Gray matter = -1.87 (-5.80, 2.05) White matter = -1.62 (-5.50, 2.26) <u>Estimated proportion of the total effect for the Pb-derived association volumes</u>: Indirect [bootstrap (1,000) estimate±SE (95% CI)]; Direct proportion estimate **Visuo-construction** **Gray matter = 0.31±0.12 (0.16, 0.62); 0.03** **White matter = 0.18±0.06 (0.08, 0.32); 0.01** **Executive Function** **Gray matter = 0.24±0.08 (0.14, 0.44); 0.02** **White matter = 0.15±0.05 (0.07, 0.29); 0.01** **Eye-hand coordination** **Gray matter = 0.19±0.07 (0.09, 0.36); 0.01** **White matter = 0.15±0.05 (0.07, 0.27); 0.01**	function score.
Prospective Canfield (2003a) Rochester, NY, USA Population may overlap with Canfield (2003b) and others	172 children born between July 1994 and January 1995, enrolled when they were 24-30 months old. Year not stated Male=47%	60.6 (1.0) months	Lifetime average = 7.4 (4.3) µg/dL Peak = 11.1 (7.1) µg/dL Concurrent = 5.8 (4.1) µg/dL Exposure measured at 6, 12, 18, 24, 36, 48 and 60 months of age	IQ measured by the Stanford-Binet Intelligence Scale at ages 3 and 5 years	Linear, polynomial, and semi-parametric models; mixed models with regression diagnostics. Childs' sex, birth weight and iron status; mother's IQ, education, race, tobacco use during pregnancy; yearly household income, HOME score.	Changes in IQ for each increase in blood Pb concentration of 1 µg/dL: <u>Lifetime average Pb</u> **at 3 years: β(SE)= -0.35 (0.17); p=0.05** **at 5 years: β(SE)= -0.57 (0.18); p=0.003** **Overall: β(SE)= -0.46 (0.15); p=0.004** <u>Peak Pb</u> At 3 years: β(SE)= -0.19 (0.10); p=0.06 **At 5 years: β(SE)=-0.26 (0.11); p=0.02** **Overall: β(SE)=-0.23 (0.09); p=0.01** <u>Concurrent Pb</u> **At 3 years: β(SE)=-0.31 (0.15); p=0.04** **At 5 years: β(SE)=-0.61 (0.19); p<0.001** **Overall: β(SE)=-0.46 (0.14); p=0.002** <u>Average Pb in Infancy (6-24 months)</u> At 3 years: β(SE)= -0.32 (0.20); p=0.10 **At 5 years: β(SE)= -0.53 (0.20); p=0.01**	Lifetime average and concurrent blood Pb was significantly associated with children's IQ scores at 3 and 5 years of age. Peak blood Pb and average Pb during infancy were significantly associated with overall IQ and IQ at 5 years,

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Overall: β(SE)=-0.43 (0.17); p=0.02	but not IQ at 3 years.
Prospective Canfield (2003b) Rochester, NY, USA Population may overlap with Canfield (2003a) and others	172 participants of an ongoing longitudinal study of the neurobehavioral effects of low-level Pb exposure, recruited as infants from lists of live births at urban hospitals. Year not stated Male= 52%	Tested at 48 months and/or 54 months.	At 48 months = 6.49 µg/dL Exposure measured when outcome assessed	Children performed the Shape School task at 48 and 54 months of age.	Bivariate correlations, general linear mixed model methods. Model covariates included: age, child's sex, birth weight, gestational age, birth order, race, maternal IQ, marital status, maternal education, prenatal smoking, household income, HOME score Model+: augmented base model including rating of attention/task orientation during the test phase and/or rating of color or shape knowledge for the practice phase Model+IQ: augmented base model with child's Stanford-Binet IQ	Efficiency Score – Control **Base Model: β = -0.017 (0.005); p< 0.01** **Model+: β = -0.008 (0.004); p< 0.05** Efficiency Score – Inhibit **Base Model: β = -0.019 (0.006); p< 0.01** Attention/task orientation – Control **Base Model: β = -0.024 (0.011); p< 0.05** Attention/task orientation – Completed Phases **Base Model: β = -0.159 (0.028); p< 0.001** **Model+: = -0.080 (0.021); p< 0.01** **Model+IQ: = -0.062 (0.022); p< 0.01** Attention/task orientation – Color knowledge **Base Model: β = -0.074 (0.014); p< 0.001** **Model+: = -0.027 (0.009); p< 0.01** **Model+IQ: β = -0.025 (0.009)** Attention/task orientation – Shape knowledge **Base Model: β = -0.057 (0.019); p< 0.01** Other models were not statistically significant.	Blood Pb at 48 months was significantly negatively associated with children's focused attention while performing the tasks, efficiency at naming colors, and inhibition of automatic responding
Prospective Canfield (2004) Rochester, NY, USA *Population may overlap with Canfield (2003b) and others*	174 children in an ongoing longitudinal study of the neurobehavioral effects of low-level Pb exposure, enrolled between 5 and 7 months from lists of live births at urban hospitals Year not stated Male = 49.4%	66.7 (1.2) months	6 months: 3.4 24 months: 9.7 60 months: 6.0 Lifetime average at 60 months: 7.2µg/dL Range = 1.4 – 19.9 Assessed semiannually from 6 to 24 months, and annually at 36, 48, and 60 months	Cognitive function as assessed by the Working Memory and Planning Battery of the Cambridge Neuropsychological Testing Automated Battery (CANTAB), tests of spatial working memory, spatial memory span, intradimensional and extradimensional shifts, and an analog of the Tower of London task.	General linear, logistic, and mixed model regressions. Child's IQ, NICU admission, maternal IQ, HOME scores, duration of breastfeeding, cigarette smoking during pregnancy, household income, average moves per year, sex of child, birth weight, maternal ethnicity, marital status, maternal education,	Associations between lifetime average blood Pb concentration and CANTAB outcomes: Big Little Circle task - % correct: **Pearson's *r* = -0.34; p≤ 0.001** **β(SE) = -0.619 (0.17); p≤ 0.001** Spatial Span task – Total non-target errors: **Pearson's *r* = 0.20; p≤ 0.01** **β(SE) = 0.145 (0.036); p≤ 0.001** Spatial Working Memory – Total errors – 6-box problems: **Pearson's *r* = 0.37; p≤ 0.05** **β(SE) = 0.456 (0.179); p = 0.016** Intradimensional and extradimensional shift task – Stages completed: **Pearson's *r* = -0.22; p≤ 0.01** **β (SE) = -0.112 (0.052); p = 0.025**	Children with higher lifetime average blood Pb showed impaired cognitive function on several measures.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
					average crowding in home, first prenatal visit.	Intradimensional and extradimensional shift task – Total trials **Pearson's *r* = 0.28; p≤ 0.01** **β (SE) = 1.40 (0.459); p = 0.003** Stocking of Cambridge task – Mean moves: **β (SE) = 0.050 (0.019); p = 0.009** Stocking of Cambridge task – Mean subsequent planning time – 2-move problems: **Pearson's *r* = 0.35; p≤ 0.001** **β (SE) = 0.142 (0.029); p < 0.001**	
Prospective Cecil (2008) Cincinnati, OH, USA *Population may overlap with Dietrich (1987) and others*	157 participants of the Cincinnati Lead Study between the ages of 19 and 24 (1979-1984) Year=2003 Male= 53%	20.8 (0.9) years	Mean of 23 measurements = 13.3 (5.9) µg/dL Range = 4.65–37.2 µg/dL Blood Pb measured every 3 months from birth to first 5 years of life, then every 6 months from 6 to 6.5 years	Global and regional changes in brain tissue were assessed using whole-brain, 3-dimensional, high resolution MRI data.	statistical analysis not reported	Percent gray matter associated with mean childhood blood Pb concentration: **Total: 1.2%; p<0.001** **Male only: 1.7%; p<0.001** Female only: p=NS	Higher mean childhood blood levels were associated with significant decrements in gray matter volume for several cortical areas overall and in males but not females.
Prospective Chandramouli (2009) United Kingdom	582 children from the Avon Longitudinal Study of Parents and Children. Year=Random sample of children born Jun – Dec 1992. Male=57%	Blood Pb measure: 30 months Evaluation of behaviour: 7 and 8 years old	4.22 (3.12) µg/dL Exposure measured at 30 months of age.	Child behavior was assessed using the Strengths and Difficulties Questionnaire, the Development And Well-being Assessment, and the Anti-social Behavior Interview. Attention was measured using the Test of Everyday Attention for Children. The educational performance of the children was captured from the results of the	Regression analyses and ordinal regression. Child's gender and IQ, maternal educational qualification and smoking, paternal socio-economic status at the time of the pregnancy, home ownership, home facilities score at 6 months, Family Adversity Index, parenting attitudes at 6 months.	<u>Regression analyses of the effect of blood Pb levels on:</u> Strengths and Difficulties Questionnaire Teacher: Hyperactivity 2–5 µg/dL, OR = 0.84 (0.47, 1.52) 5–10 µg/dL, OR = 1.25 (0.67, 2.33) **>10 µg/dL, OR =2.82 (1.08, 7.35)(*p*=0.03)** Teacher: Total Difficulties 2–5 µg/dL, OR =1.02 (0.58, 1.79) 5–10 µg/dL, OR =1.30 (0.71, 2.37) **>10 µg/dL, OR =2.69 (1.06, 6.81)(*p*=0.04)** Parent: Hyperactivity 2–5 µg/dL, OR = 0.88 (0.58, 1.78) 5–10 µg/dL, OR = 1.24 (0.79, 1.97) >10 µg/dL, OR = 1.30 (0.62, 2.71) Parent: total difficulties 2–5 µg/dL, OR = 1.13 (0.74, 1.72) 5–10 µg/dL, OR = 1.27 (0.81, 2.01) >10 µg/dL, OR = 1.20 (0.57, 2.51) Development and Well-being Assessment	Blood Pb at 30 months was significantly associated with hyperactivity, as assessed by teachers, antisocial behavior and lower writing and reading scores at 7 to 8 years old.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				national Standard Assessment Tests (SATs).		Activity score 2–5 µg/dL, OR = 0.81 (0.50, 1.29) 5–10 µg/dL, OR = 1.24 (0.77, 2.01) >10 µg/dL, OR = 0.96 (0.44, 2.10) Attention score 2–5 µg/dL, OR = 0.83 (0.52, 1.32) 5–10 µg/dL, OR = 1.28 (0.79, 2.06) >10 µg/dL, OR = 1.15 (0.54, 2.47) Anti-social Behavior Interview Anti-social Activities 2–5 µg/dL, OR = 0.93 (0.47, 1.83) 5–10 µg/dL, OR = 1.44 (0.73, 2.84) **>10 µg/dL, OR = 2.90 (1.05, 8.03)(*p*=0.04)** Test of Everyday Attention for Children Selective attention 2–5 µg/dL, OR = 1.03 (0.66, 1.61) 5–10 µg/dL, OR = 0.99 (0.62, 1.57) >10 µg/dL, OR = 1.14 (0.54, 2.40) Dual attention 2–5 µg/dL, OR = 1.13 (0.66, 1.91) 5–10 µg/dL, OR = 1.22 (0.70, 2.14) >10 µg/dL, OR = 0.48 (0.20, 1.13) Same worlds 2–5 µg/dL, OR = 0.99 (0.64, 1.53) 5–10 µg/dL, OR = 1.31 (0.82, 2.08) >10 µg/dL, OR = 1.48 (0.69, 3.15) Opposite worlds 2–5 µg/dL, OR = 1.29 (0.83, 2.01) 5–10 µg/dL, OR = 1.26 (0.79, 2.03) >10 µg/dL, OR = 1.04 (0.49, 2.21) Standard Assessment Tests Reading 2–5 µg/dL, OR = 0.88 (0.54, 1.43) **5–10 µg/dL, OR = 0.51 (0.32, 0.82); p=0.006** >10 µg/dL, OR = 0.62 (0.28, 1.35) Writing 2–5 µg/dL, OR = 1.08 (0.69, 1.71) **5–10 µg/dL, OR = 0.49 (0.31, 0.78); p=0.003** **>10 µg/dL, OR = 0.44 (0.21, 0.93); p=0.031** Spelling 2–5 µg/dL, OR = 1.41 (0.78, 2.53) 5–10 µg/dL, OR = 0.76 (0.40, 1.42) >10 µg/dL, OR = not reported Mathematics 2–5 µg/dL, OR = 1.38 (0.86, 2.20)	

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						5–10 µg/dL, OR = 0.73 (0.46, 1.15) >10 µg/dL, OR = 0.86 (0.41, 1.81)	
Prospective Chen (2005) USA *Population may overlap with Chen (2007)*	780 children in the Treatment of Lead-exposed Children (TLC) Study who had blood Pb levels of 20-44 µg/dL at age 12-33 months; Year not stated % male not stated	2 to 7 years	Pre-treatment baseline (~age 2): 26.2 (5.1) Age 5: 12 (5.2) Age 7: 8.0 (4.0) Peak (2-7): 30.6 (6.6) Average (age 2 to 5): 17 (5) Average (age 2 to 7): 14.4(4.6) Up to 24 Pb measures: before randomization; on days 7, 28, and 42 after the beginning of each course of treatment; and every 3-4 months after treatment stopped	Intelligence assessed by Bayley Scales of Infant Development (BSID-II) at age 2; the Wechsler Preschool and Primary Scales of Intelligence Scale for Children (WPPSI-R) at 5 years old; and the Wechsler Intelligence Scale for Children at 7 years old.	Multiple linear regression models. Clinical center, race, gender, language, parent's education, parent's employment, single parent, caregiver's IQ, and exact age at both blood Pb measurements.	<u>Adjusted estimates (95% CI) of a 10 µg/dL increase in Pb on change on IQ test scores:</u> **Age 2 Pb and MDI at baseline: - 2.9 (-4.7, -1.0)** **Age 2 Pb and IQ at 5: -2.3 (-4.1, -0.5)** **Age 5 Pb and IQ at 5: -3.5 (-5.3, -1.7)** **Aver. (2-5) Pb and IQ at 5: -2.9 (-4.8, -1.0)** Age 2 Pb and IQ at 7: -1.1 (-2.9, 0.7) **Age 5 Pb and IQ at 7: -2.9 (-4.8, -1.1)** **Age 7 Pb and IQ at 7: -5.4 (-7.8, -2.9)** Peak Pb and IQ at 7: -0.7 (-2.1, 0.7) **Aver. (2-7) Pb and IQ at 7: -3.3 (-5.4, -1.1)** <u>Adjusted estimates (95% CI) of a 10 µg/dL increase in prior and concurrent Pb on change on IQ test scores:</u> Age 2 and Age 5 Pb with IQ at 5: No score adj: 2=-1.2 (-3.1, 0.7); **5=-2.9 (-4.9, -0.9)** Base MDI adj: 2=-0.1 (-1.8, 1.5); **5=-2.4 (-4.1, -0.7)** Age 2 and Age 7 Pb with IQ at 7: No score adj: 2=0.1 (-1.8, 2.0); **7=-5.0 (-7.6, -2.4)** Base MDI adj: 2=-0.4 (-1.4, 2.1); **7=-3.8 (-6.2, -1.4)** Age 5 and Age 7 Pb with IQ at 7: No score adj: 5=-1.2 (-4.1, 1.7); **7=-3.9 (-7.4, 0.0)** Age 5 IQ adj: 5=1.7 (-0.3, 3.6); **7=-3.7 (-6.3, -1.1)** <u>Adjusted estimates of regression coefficients(95% CI) of categorical blood Pb in models for IQ scores</u>: mean; est. IQ at age 5, blood Pb at ages 2 and 5: 2 (Pb<24.9), 5 (Pb<11.4): 83.7; Referent **2 (Pb<24.9), 5 (Pb≥11.4): 78.8; -2.9 (-5.8, 0.1)** 2 (Pb≥24.9), 5 (Pb<11.4): 82.4; 0.4 (-2.5, 3.3) **2 (Pb≥24.9), 5 (Pb≥11.4): 77.6; -4.0 (-6.6, -1.5)** IQ at age 7, blood Pb at ages 2 and 7: 2 (Pb<24.9), 7 (Pb<7.2): 89.3; Referent **2 (Pb<24.9), 7 (Pb≥7.2): 84.6; -3.6 (-6.4, -0.7)** 2 (Pb≥24.9), 7 (Pb<7.2): 88.9; 0.0 (-2.8, 2.7) **2 (Pb≥24.9), 7 (Pb≥7.2): 84.0; -3.7 (-6.2, -1.3)** IQ at age 7, blood Pb at ages 5 and 7: 5 (Pb<11.4), 7 (Pb<7.2): 89.4; Referent 5 (Pb<11.4), 7 (Pb≥7.2): 85.9; -2.3 (-5.9, 1.3) 5 (Pb≥11.4), 7 (Pb<7.2): 88.2; 0.3 (-3.1, 3.7) **5 (Pb≥11.4), 7 (Pb≥7.2): 83.9; -3.8 (-6.0, -1.6)**	Concurrent blood Pb levels were significantly associated with lower intelligence test scores at ages 2, 5, and 7 with the estimates increasing with age. Age 5, but not age 2, blood Pb was significantly associated with lower intelligence test scores at age 7. The authors conclude that peak blood Pb does not fully account for the observed association in older children between their lower blood Pb concentrations and IQ

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Chen (2007) USA *Population may overlap with Chen (2005)*	780 children in the Treatment of Lead-exposed Children (TLC) Study who had blood Pb levels of 20-44 µg/dL at age 12-33 months; Year not stated Male=56%	7 (0.5) years	26 (5.1) µg/dL at baseline (age 2) 12 (5.2) µg/dL at 5-year follow-up 8.0 (4.0) µg/dL at 7-year follow-up Measured at age 2 (baseline), age 5 and age 7	The Connors Parent Rating Scale (CPRS-R) and the Wechsler Preschool and Primary Scales of Intelligence Scale for Children (WPPSI-R) at 5 years old; the Behavior Assessment System for Children teacher rating and parent rating scales (BASC-TRS and BASC-PRS), and the Wechsler Intelligence Scale for Children at 7 years old.	Path (regression) analysis, logistic regression analysis, spline regression. Clinic center, race, sex, language, parent's education, parent's employment, single parent, exact age at blood Pb concentration measurement, caregiver's IQ, (and 7-year IQ in direct effect models only)	Indirect effects of 10 µg/dL blood Pb concentration at age 5 on behavioral test scores (CPRS-R) at age5, adjOR (95% CI): **Oppositional Index: 0.35 (0.02, 0.68); p<0.05** **Hyperactivity Index: 0.34 (0.05, 0.63); p<0.05** ADHD Index: 0.61 (-0.39, 1.61); NS Behavioral Index: 0.44 (-0.46, 1.34); NS After controlling for IQ (direct effect), the none of the associations were significant Indirect effects of 10 µg/dL blood Pb concentration at age 2 on behavioral test scores (CPRS-R) at age5, adjOR (95% CI): **ADHD Index: 0.90; p<0.05** **Behavioral Index: 0.64 (0.23, 1.05); p<0.05** There was no association with Oppositional Index and Hyperactivity Index. After controlling for IQ (direct effect), the none of the associations were significant AdjOR (95% CI) for BASC scores $\geq$ 60 per 10 µg/dL blood Pb concentration at age 7: BASC-TRS Behavioral symptoms = 1.25 (0.90, 1.73); NS **Externalizing problems = 1.42 (1.03, 1.97); p<0.05** Internalizing problems = 1.07 (0.76, 1.52); NS **School problems = 1.39 (1.05, 1.86); p<0.05** BASC-PRS **Behavioral Symptoms = 1.52 (1.13, 2.05); p<0.05** Externalizing problems = 1.27 (0.96, 1.68); NS Internalizing problems = 0.98 (0.69, 1.40); NS Authors state that at age 7 there were no statistically significant direct or indirect effects of blood Pb concentration at age 2 [data not shown].	Concurrent blood Pb was significantly associated with Oppositional and Hyperactivity Indexes at age 5 and Externalizing Problems, School Problems and Behavioral Symptoms at age 7. Blood Pb at age 2 was associated with ADHD and Behavioral Indexes at age 5, but no measures at age 7.
Cross-sectional Chiodo (2004) Detroit, MI, USA *Population may overlap with (Chiodo et al. 2007)*	246 African American inner-city children of mothers recruited while pregnant; Year not stated Male=60%	7.8 (0.3) years (range = 7.2 – 8.9 years).	5.4 (3.3) µg/dL (range = 1 – 25 µg/dL Blood Pb measured at 7.5 years of age	Intelligence was assessed by (WISC-III IQ), reaction time, visual–motor integration (Grooved Pegboard Test), fine motor skills, attention (Mirsky's Attention Battery), and teacher-reported withdrawn behaviors	Nonparametric regression plots, multiple regression analysis, Pearson correlation. Primary caregiver's socioeconomic status, age, marital status, vocabulary, level of depression,	Relation of blood Pb levels to neurobehavioral measures at age 7.5: WISC-III IQ **Full IQ: β = -0.20; p$\leq$ 0.01** **Verbal IQ: β = -0.14; p$\leq$ 0.05** **Performance IQ: β = -0.21; p$\leq$ 0.001** Mirsky's Attention Battery: **CPT – visual, number correct** **β = -0.14; p$\leq$ 0.05** **Working Memory – Seashore rhythm** **β = -0.15; p$\leq$ 0.05**	Blood Pb was significantly associated with lower IQ and multiple other measurements of neuro-behavioral deficits at age 7.5 years.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				(Achenbach Child Behavior Checklist and Barkley-DuPaul Attention Deficit Hyperactivity Disorder Scale).	psychological symptoms (anxiety and hostility); number of children in the household, HOME score, crowded living conditions, disruption in care-giving, Family Environment Scale (FES), Life Events Scale for the primary caregiver (LES) and for the child (LES-C); child's gender and parity.	**Working Memory – WISC-III digit span** **β = -0.13; p≤ 0.05** **Executive Function – Conceptual Level** **β = -0.31; p≤ 0.05** **Executive Function – Conceptual Level** **β = -0.30; p≤ 0.05** Beery Visual – motor integration: **β = -0.20; p≤ 0.01** Matching Familiar Figures – number correct: **β = -0.19; p≤ 0.01** Peg Board – Number of pegs dropped: **β = 0.17; p≤ 0.01** *Mental Rotation – Backward reaction time:* **β = 0.14; p≤ 0.05** Magnitude Est. – Numbers reaction time **β = 0.15; p≤ 0.05** Barkley – DuPaul ADHD Scale: ADHD score **β = 0.16; p≤ 0.05** Inattention factor **β = 0.18; p≤ 0.05** Child Behavior Checklist: Attention **β = 0.15; p≤ 0.05** Thought Problems **β = 0.18; p≤ 0.05** Barkley Direct Observation - Off Task: **β = 0.14; p≤ 0.05**	
Cross-sectional (Chiodo *et al.* 2007) Detroit, MI, USA *Population may overlap with (Chiodo et al. 2004)*	506 African American inner-city children of mothers recruited while pregnant; Year=births between 1989 and 1991 Male=50.8%	7 years	5.0 (3.0) Measured at the 7-year follow-up	Wechsler Primary and Preschool Scale of Intelligence-Revised (WPPSI-R) and the Test of Early Reading Ability; total reading and math scores measured by the Metropolitan Achievement Test; sustained attention by the Conner's Continuous Performance Test (CPT); PROBS-14; Teacher Report Form (TRF); Test of Early	Regression analyses Prenatal drug exposures	Relation between child outcome and Pb (β): PROBS-14 **Central Processing: β=0.18; p<0.001** **Hyperactivity: β=0.13; p<0.01** TRF **Attention problems: β=0.13; p<0.01** Social problems: β=0.10; p<0.10 Delinquent behavior: β=0.09; p<0.10 Total behavior problems: β=0.09; p<0.10 Appropriate behavior: β=-0.09; p<0.10 Hard working: β=-0.10; p<0.10 **Math performance: β=-0.12; p<0.01** Reading performance: β=-0.10; p<0.10 CPT **Reaction time: β=0.15; p<0.001** Conner's Teacher Rating Scale: Attention factor: β=0.12; p<0.10	Blood Pb was significantly associated with neurobehavioral deficits including lower IQ, math scores, and early reading ability and higher central processing, hyperactivity, reaction time, and more attention problems.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				Reading Ability		Impulsivity factor: β= 0.04; NS **Test of early reading ability: β=-0.14; p<0.001** MAT **Math: β=-0.17; p<0.001** Reading: β=-0.06; NS WPPSI **Verbal IQ: β=-0.17; p<0.001** **Performance IQ: β=-0.16; p<0.001** **Full IQ: β=-0.19; p<0.001**	
Cross-sectional Cho (2010) Korea *Second phase of Kim(2009)*	639 third and fourth grade children from schools in each town: Seoul, Ulsan, Incheon, Seongnam, and Yeoncheon; Year = 2008 Male = 52.1%	9.05 (0.72) Range: 8-11	1.9 (0.67)µg/dL Range: 0.53-6.16 Boys: 2.02µg/dL Girls: 1.82µg/dL	Inattention-hyperactivity and neurocognitive profiles: teachers and parents completed the Korean version of the ADHD Rating Scales, and the children performed the Korean Educational Development Institute–Wechsler Intelligence Scales (KEDI-WISC) and a neurocognitive battery consisting of the continuous performance test (CPT), the Children's Color Trails Test (CCTT), and the Stroop Color–Word Test *Also measured urinary cotinine (mean = 5.8ng/mL)*	Linear regression Adjusted for age, gender, paternal education, maternal IQ, child IQ, residential area, and birth weight *Additionally adjusted for urinary cotinine*	<u>Association of ADHD, neurocognition and blood Pb</u>: *ß*, *p* ADHD rating scale **Inattention, teacher: 0.157, *p* < 0.001** **Hyperactivity, teacher: 0.179, *p* < 0.001** **Total, teacher: 0.176, *p* < 0.001** Inattention, parent: 0.056, *p* = 0.249 Hyperactivity, parent: 0.073, *p* = 0.132 Total, parent: 0.067, p = 0.165 Continuous Performance Test Omission errors: 0.035, *p* = 0.457 **Commission errors: 0.093, *p* = 0.044*** ***Adjusted for cotinine: 0.077, *p* = 0.101 Response time: -0.020, *p* = 0.679 Response time variability: 0.055, *p* = 0.239 *When Stroop Word and Color Test Word reading: : 0.037, *p* = 0.421 Color naming: : 0.021, *p* = 0.651 Color−word: : -0.003, *p* = 0.947 Interference: : -0.037, *p* = 0.461 Children's Color Trail Test CCTT-1 total time: : 0.021, *p* = 0.663 CCTT-2 total time: : -0.021, *p* = 0.650 Difference interference: : 0.050, *p* = 0.301 *Adjustment for urinary cotinine did not significantly change Pb results other than CPT commission errors.* *Cotinine was associated with several neurocognitive functions (but not ADHD) after adjustment for blood Pb.*	Concurrent blood Pb was associated with teacher reports of ADHD symptoms including inattention and hyperactivity, but an association with one neurocognition measure was confounded by urinary cotinine. Urinary cotinine was also significantly associated with poorer performance on several measures of cognitive performance after adjusting for blood Pb
Case-control Chuang (2007) Kaohsiung, Taiwan	294 male factory workers (121 with an average hearing threshold over 25 dB and 173 with	39.4 (9.8) years <u>Cases</u>: 44.3 (8.6) years	Geom mean (SD) <u>Cases</u>: 10.662 (0.370) Range: 0.18-96.3	Hearing threshold 16hrs after the end of the last working day	Mann-Whitney nonparametric test <u>Average hearing</u> threshold of each ear:	Pb was higher in the cases, p<0.001 <u>Average hearing threshold and logPb (µg/L)</u>: β (SE), p-value **Right (0.5k+1k+2k)/3: 6.14 (1.40), p<0.001**	Blood Pb levels were higher in cases with hearing loss and positively

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	normal hearing), selected from hospital-based occupational health examinations; Year =2003-2004 Male = 100%	Controls: 35.9 (9.2) years	Controls: 3.902 (0.203) Range: 0.80-47.1 *text and abstract have slightly different values than Table 3 shown here	*Also measured blood Mn, As, and Se*	multiple regression Hearing threshold: mixed regression model Adjusted for age, smoking, alcohol, years exposed to noise, logMn, logAs, and logSe. Mixed model also included left vs right ear and pure tone frequency	**Left (0.5k+1k+2k)/3: 7.99 (1.57) p<0.001** **Right (0.5k+1k+2k+3k+4k+6k)/6: 4.43 (1.54), p=0.004** **Left (0.5k+1k+2k+3k+4k+6k)/6: 6.06 (1.66) p<0.001** Age was significantly positively associated (p<0.001) and logSe was significantly negatively associated (p: 0.113-0.005) in the model Hearing threshold: β (SE), p-value **logPb (µg/L): 7.11 (1.33), p<0.001** **Age (yr): 0.47 (0.07), p<0.001** **logSe (µg/L): -10.83 (5.05), p=0.033**	associated with hearing threshold
Case control Coon (2006) Detroit, MI, USA	121 Parkinson's Disease (PD) patients and 414 age-, sex-, and race-frequency-matched controls from the Henry Ford Health System; Year=1995-1999 Male cases=62.8% Male cont.=54.8%	69.9 (8.2)	Blood Pb: mean not reported Environmental Pb exposure (% of time exposed while at work): High: 90% Moderate: 10-90% Low: <10% Tibia and calcaneal bone Pb (µg/g) Range: 0-200, Lifetime Pb exposure by model including blood and bone Pb	Parkinson's Disease: International Classification of Disease, 9th revision (ICD-9)codes 332 and 332.0	Multiple logistic regression; chi-square Age, sex, race, smoking, and coffee and alcohol consumption	Risk of PD: Adj.OR (95% CI) Whole body lifetime Pb exposure (quartiles) 1st: reference 2nd: 1.90 (0.97, 3.71); p=0.060 3rd: 1.71 (0.86, 3.41); p=0.125 **4th: 2.27 (1.13, 4.55); p=0.021** Tibia (quartiles) 1st: reference 2nd: 0.87 (0.43, 1.75); p=0.691 3rd: 1.33 (0.70, 2.52); p=0.387 4th: 1.62 (0.83, 3.17); p=0.160 Calcaneus (quartiles) 1st: reference 2nd: 1.71 (0.91, 3.20); p=0.094 3rd: 1.12 (0.57, 2.22); p=0.737 4th: 1.50 (0.75, 3.00); p=0.253	The risk of PD in individuals in the highest quartile for lifetime Pb exposure was significantly twices that of individuals in the lowest quartile. There was no association of PD with bone Pb.
Prospective Cooney (1989a) Sydney, Australia *Population may overlap with Cooney (1989b)*	N=215-274 from the Sydney Lead Study; Year=born between 1982-1983 % male not stated	6, 12, 24, and 36 months	Maternal at delivery: 9.1; Range 3-28 (70% ≤ 10µg/dL) Cord: 8.1; range 1-36 (80% ≤ 10µg/dL) Blood also measured in 6, 12, 18, 24, 30, and 36 month s	Development assessed by the Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores of the Bayley Scales of Infant Development at 6, 12 and 24 months, and General Cognitive Index (GCI) score from the McCarthy Scales of Children's Abilities	Multiple regression Maternal age, maternal verbal intelligence, maternal education, maternal smoking, maternal alcohol use, paternal age, paternal education, paternal occupation, birth-weight, gestational age, obstetrical complications, and postnatal factors, and current HOME score	Simple correlation with maternal and cord blood Pb and incremental effect of Pb: mat., cord corr; ΔR^2; *P* 6 months, BSID Mental: -0.044, -0.161; ΔR^2= 0.008; p>0.25 PDI: 0.035,0.025; ΔR^2=0.003; p>0.60 12 months, BSID MDI: 0.015; **0.153 (p<0.05)**; ΔR^2=0.008, p>0.30 PDI: 0.081; **0.167 (p<0.05)**; ΔR^2=0.019; p>0.05 24 months, BSID MDI: 0.006, 0.053; ΔR^2=0.001; p>0.70 PDI: 0.021, -0.060; ΔR^2= 0.013; p>0.20 36 months, MSC GCI: 0.040, 0.045; ΔR^2=0.001; p>0.70 Motor score: 0.015, 0.010; ΔR^2=0.001; p>0.90	Maternal blood and cord blood Pb were not significantly associated with mental or psychomotor developmental deficits at 6, 12, 24, or 36 months.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				and motor subscale at 36 months		No significant relationships were found when four birth outcomes (birth-weight, gestational age, obstetrical complications, and postnatal factors) were regressed on maternal and cord blood Pb levels	
Prospective; Sydney, Australia; Cooney (1989b) *Population may overlap with Cooney (1989a)*	207 children from the Sydney Lead Study Year=born between 1982 and 1983 % male not stated	48 months	Maternal: 9.1(1.3) Cord: 8.1(1.4) 6 months: 15.0 (1.6) 12 months: 15.4 (1.5) 18 months: 16.4 (1.5) 24 months: 15.2 (1.5) 30 months: 12.8 (1.8) 36 months: 12.0 (1.5) 42 months: 10.7 (1.5) 48 months: 10.1 (1.4) Prenatal includes maternal and cord	General Cognitive Index (GCI) score from the McCarthy Scales of Children's Abilities (MSCA) and motor subscale	Correlation, Regression Analysis of covariance (ANCOVA) Gestational age, verbal ability, education of mother, education and occupational status of father, and the HOME total score at 48 months	<u>Correlations between blood Pb and MSCA scores at 48 months:</u> Maternal: GCI r=-0.008; Motor r=-0.029 Cord: GCI r=0.109; Motor r=-0.025 6 months: GCI r=0.080; Motor r=-0.022 12 months: GCI r=0.130; Motor r=0.118 18 months: GCI r=0.050; Motor r=0.057 24 months: GCI r=-0.034; Motor r=-0.040 30 months: GCI r=0.095; Motor r=-0.067 36 months: GCI r=-0.060; Motor r=-0.131 42 months: GCI r=0.030; Motor r=-0.057 48 months: GCI r=-0.028; Motor r=0.005 None of the correlations are significant (p>0.05) Correlations between composite blood Pb levels and MSCA scores at 48 months: 1st yr: **GCI r^2=0.160; p<0.05**; Motor r^2=0.056 2nd yr: GCI r^2=0.016; Motor r^2=0.037 3rd yr: GCI r^2=0.029; Motor r^2=-0.097 4th yr: GCI r^2=-0.010; Motor r^2=-0.026 <u>Adjusted regression of MSCA scores at 48 months on current and previous blood Pb levels</u>: Prenatal: GCI r^2=0.009; p=0.14, Motor r^2=0.002; p=0.55 1st yr: GCI r^2=0.013; p=0.07, Motor r^2=0.001; p=0.67 2nd yr: GCI r^2=0.002; p=0.60, Motor r^2=0.004; p=0.33 3rd yr: GCI r^2=0.003; p=0.76, Motor r^2=0.006; p=0.26 4th yr: GCI r^2=0.001; p=0.76, Motor r^2=0.001; p=0.96 All: GCI r^2=0.0028; p=0.14, Motor r^2=0.018; p=0.56 <u>ANCOVA: Incremental effect of Pb on change in developmental outcome from 36 to 48 months</u>: Current Pb exposure (4th year): GCI r^2=0.004; p=0.36, Motor r^2=0.000; p=0.96 Current and Previous Pb exposure : GCI r^2=0.028; p=0.14, Motor r^2=0.018; p=0.56	Prenatal and postnatal blood Pb was not associated with lower developmental indices at 48 months of age.
Prospective Coscia (2003) Cincinnati, OH USA *Population may overlap with*	196 participants from the Cincinnati Lead Study (CLS) Year=1979-1984 Male= 47%	1st assessment 6.55 (0.12) years 2nd assessment 11.40 (1.04) years	Means over spans: Prenatal: 8.53 (3.90) 1st yr: 10.73 (5.13) 2nd yr: 17.03 (8.13) 3rd yr: 16.25 (7.31) 4th yr: 14.30 (12.02) 5th yr: 12.02 (6.20)	Cognitive development at ages 6.5, 11, and 15 measured by Vocabulary and Block Design and Wechsler Intelligence Scales	Backward Elimination Regression Analysis Fetal distress and growth, perinatal complications, and maternal IQ;	<u>Blood Pb at age 15 years and vocabulary scores at ages 6.5, 11, and 15 years (growth curve analysis)</u>: **Main effect: β (SE)= -4.01 (1.78)** **Linear Effect: β (SE)= 0.95 (0.35)** **Quadratic Effect: β (SE)= -0.05 (0.02)** Other statistically significant covariates retained in the models include: age, birthweight, SES after age 11,	Blood Pb at age 15 was significantly associated with lower verbal comprehension scores and a

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Dietrich (1987) and others		3rd assessment 15.5 (0.85) years	6th yr: 9.78 (5.18) Yrs 1-6: 13.46 (5.87) @ 6.5 yrs: 8.27 (4.67) @ 15 yrs: 2.80 (1.29)	for Children.	socioeconomic status, HOME inventory at 6, 12, 24 and 36 months.	maternal IQ, and HOME score. None of the other Pb measures were statistically significant. None of the Pb measures were statistically significantly related to Block Design Scores.	greater decline in vocabulary development at age 15; blood Pb (at any age) was not associated with perceptual organization test scores
Cross-sectional Counter (2008) Ecuador	166 children aged 6 – 16 years exposed to Pb in a ceramic glazing cottage industry in high altitude villages; Year not stated Male= 49%	[mean age not stated] Range = 6 – 16 years	Blood Pb = 18 (15.1) µg/dL Range 3-86 ZPP/heme ratio = 105.7 (100.9) µmol/mol (normal reference range = 30-69 µmol ZPP/mol heme) Current blood Pb levels	Auditory memory/attention was assessed using the Digit Span subtest of the Wechsler IV intelligence scale.	Student's *t*-test; regression analyses	Correlation between log blood Pb and Digit span scale score: **r = 0.251; p = 0.001** Correlation between logZPP/ heme ratio (a chronic measure of exposure) and Digit span scale score: **r = 0.246; p = 0.001**	Blood Pb and ZPP levels were significantly associated with poor performance on a test of auditory memory.
Cross-sectional Despres (2005) Quebec, Canada *Population may overlap with Boucher (2009)*	110 Preschool Inuit children aged 4 to 6 Nunavik, Quebec; follow-up of the Cord Blood Monitoring Program conducted (1993 – 1996) with no known neurological or developmental disorder, and no severe chronic disease; Year= 4-6 years after 1993-1996 program Male= 45%	5.4 (0.4) years	Cord = 5.0 (4.1) (range = 0.8 - 27.1) *sig. correlation with PCB153 Venous blood at testing = 5.4 (5.0) (range = 1.0 - 37.1) Correlation between cord and age 5 blood Pb: 0.23 (p<0.05)	Motor functions were assessed with quantitative tests for sub-clinical detection of movement disorders: Catsys system measured postural hand tremor, reaction time, and postural sway; the Sway Analysis Test System; Rapid pointing and alternating arm movements Neurological function measured with the Amiel-Tison and Gosselin examination and gross motor	Multiple hierarchical linear regression (p≤0.1 remained in model) Mother's age, socioeconomic status, reproductive history, education, psychological distress, nonverbal reasoning abilities; number of children and adults at home, intra-family violence, HOME Inventory; child's head circumference, height, weight, BMI, duration of breastfeeding, iron deficiency, prenatal exposure to alcohol, illicit drugs or tobacco.	Hierarchical linear regression for neuromotor variables and concurrent childhood Pb*:* Pearson *r*; *β*; Reaction Time (n=93): ***r* = 0.21, p≤ 0.05; *β* = 0.24, p≤ 0.01;** Model included age, HOME, maternal education, breastfeeding, and head circumference **Model *F* = 8.89, p≤0.001**; R^2 = 0.38 Sway (static) Velocity (n=96): ***r* = 0.24, p≤ 0.01; *β* = 0.24, p≤ 0.05** Model included only childhood Pb **Model *F* =5.75, p≤0.05**; R^2 = 0.06 Sway (static) Sagittal (n=97): ***r* = 0.22, p≤ 0.05; *β* = 0.22, p≤ 0.05** Model included only childhood Pb **Model *F* =4.90, p≤0.05**; R^2 = 0.05 Sway (balance) Tandem (sagittal sway) (n=88): ***r* = 0.19, p≤ 0.05; *β* = -0.18 ; p≤ 0.10** Model included weight and maternal education **Model *F* =3.77, p≤ 0.05;** R^2 = 0.12 Sway (balance) Tandem (transversal sway) (n=87): ***r* = 0.22, p≤ 0.05; β = 0.26, p≤ 0.05**	Concurrent blood Pb was significantly associated with changes in reaction time, sway oscillations, alternating arm movements and action tremor, but not gross motor development or neurological function#623.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				functions examined with 10 motor tasks Also measured PCB congeners, aldrin, β-HCH, DDE, DDT, Mirex, Hexachlorobenzene, Chlordane, *Cis*-Nonachlor, *Trans*-Nonachlor, Oxychlordane, and Hg		Model included weight and child PCB153 **Model *F* =4.41, p≤ 0.01;** R^2 = 0.14 Alt. Movements, Coefficient of Variation (n=99): ***r* = 0.24, p≤ 0.01; β = 0.22, p≤ 0.05** Model included alcohol during pregnancy **Model *F* =4.99, p≤ 0.01;** R^2 = 0.09 Alt. Movements, Coherence Between Hands (n=105): ***r* = -0.29, p≤ 0.001; β = -0.29, p≤ 0.01** Model included only childhood Pb **Model *F* =9.65, p≤0.01,** R^2 = 0.09 Alt. Movements, Synkinesis (n=104): ***r* = 0.24, p≤ 0.01; β = 0.23, p≤ 0.05** Model included maternal age and head circumference **Model *F* =4.80, p≤0.01,** R^2 = 0.13 Pointing Movements, Tremor (n=99): ***r* = 0.32, p≤ 0.001; β = 0.24 ; p≤ 0.05** Model included childhood Hg **Model *F* =7.61, p≤0.001,** R^2 = 0.14 Gross motor development and neurological examination were unaffected by prenatal and postnatal Pb exposure (data not shown)	
Prospective Dietrich (1987) Cincinnati, OH, USA *Population may overlap with Dietrich (1990) and others*	266 mothers and 96 children ages 3 to 6 months residing in pre-designated Pb-hazardous areas of Cincinnati Lead Study (CLS) Year=1979-1984 Male= 50.2%	3 and 6 months	Prenatal (maternal): 8.0(3.7) Cord: 6.4(4.5) Maternal exposure measured (1st trimester-50%, 2nd trimester-49%, 3rd trimester-1%); cord measured at birth (cord)	Behavioral development as assessed by the Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores of the Bayley Scales of Infant Development.	Multiple regression Birth weight, gestation, maternal age, child race, child sex, and socioeconomic status	Parameter estimates for fetal Pb exposure variables on MDI and PDI: β (SE) <u>Maternal Prenatal</u> **MDI at 3 months: -0.34 (0.17); p=0.05** **MDI at 6 months - 0.76 (0.34); p=0.02** PDI: No significant effects of prenatal Pb exposure. <u>Cord</u> **MDI at 3 months: -0.60 (0.26); p=0.02** MDI at 6 months: -0.66 (0.37); p = 0.08 PDI: No significant effects of cord Pb exposure	Maternal prenatal blood Pb was significantly associated with deficits in MDI at 3 and 6 months. Cord blood Pb was significantly associated with deficits in MDI at 3 months; Neither was associated with PDI
Prospective Dietrich (1990) Cincinnati, OH, USA	237 2-year old subjects from the Cincinnati Lead Study Cohort; Year=births	24 months	Prenatal (maternal): 8.0 (3.7) 24-month blood Pb: 17.45 (9.16)	Behavioral development as assessed by the Bayley Mental Development Index	Multiple regression analyses Birth weight, gestational age,	<u>Association between blood Pb level and performance on the Bayley MDI at 24 months of age</u>: β(SE) **Maternal prenatal Pb: 0.5058 (0.2188); p=0.0217** 24 months blood Pb: 0.1270 (0.0877); p=0.1490	Prenatal blood Pb levels were significantly associated with MDI scores at

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Population may overlap with Dietrich (1987) and others	between 1979-1984 % male not stated			(MDI).	Obstetrical Complications Scale, Postnatal Complications Scale, child sex, child race, composite index of tobacco and alcohol consumption, maternal age, socioeconomic status, and parity		24-months. Blood Pb at 24 months was not significantly associated with MDI scores.
Prospective Dietrich (1991) Cincinnati, OH, USA *Population may overlap with Dietrich (1987) and others*	258 children from the Cincinnati Lead Study (CLS) cohort at age 4; Year=births between 1979-1984 Male= 50.8%;	4 years	Prenatal (maternal blood Pb measured at first prenatal visit): 75% of women= ≤10 Neonatal (10 days old): 75% of newborns=≤7 Postnatal: Mean lifetime blood Pb (quartiles): 1st: 7.9 2nd: 11.4 3rd: 15.2 4th: 23.7	Kaufman Assessment Battery for Children (K-ABC), subscales: Mental Processing Composite standard score (MPC); Sequential Processing standard score (SEQ); Simultaneous Processing standard score (SIM); Non-verbal standard score (NONVB); Achievement standard score (ACHIV)	Backward and forward stepwise multiple regression; bivariate regression Birth weight, maternal cigarette use during pregnancy, maternal marijuana use during pregnancy, child race, and preschool attendance	<u>Regression coefficients for blood Pb indices and K-ABC mental processing subscales and achievement</u>: β <u>MPC</u> Prenatal: 0.11; p=ns **Neonatal*:-0.63; p≤0.01** Postnatal:-0.07; p=ns <u>SEQ</u> Prenatal:0.20; p=ns **Neonatal*:-0.68; p≤0.01** Postnatal: 0.00; p=ns <u>SIM</u> Prenatal: 0.01; p=ns **Neonatal*:-0.50; p≤0.05** Postnatal: -0.12; p=ns <u>NONVB</u> Prenatal:-0.08; p=ns **Neonatal*: -0.63; p≤0.01** Postnatal: -0.0; p=ns <u>ACHIV</u> Prenatal: 0.04; p=ns **Neonatal*: -0.28; p≤0.05** Postnatal:0.07; p=ns *neonatal level by social class interaction model	Blood Pb at 10 days old was significantly associated with cognitive function with a social class interaction.
Prospective Dietrich (1992) Cincinnati, OH, USA *Population may overlap with Dietrich (1987) and others*	259 subjects from the Cincinnati Lead Study Cohort; Year=births between 1979-1984 % male not stated	5 years	Maternal prenatal: 8.2 (3.8) Newborn (10 days): 4.8 (3.3) Mean 1st year: 10.6 (5.1) Mean 2nd year: 17.2 (8.4) Mean 3rd year: 16.3 (7.8) Mean 4th year: 14.1 (7.3)	Neurobehavioral assessment: a Screening Test for Auditory Processing Disorders(SCAN) at 57 months including the Filtered Word Subtest (FWS) and the Auditory Figure-Ground Subtest (AFGS) [Left (L), Right (R), and Total(T)] the	Multiple regression SCAN test regression adjustments included hearing screen, social class, HOME scores, birth weight, gestational age, obstetrical complications scale score, and alcohol consumption	<u>Adjusted regression coefficients for blood Pb indices and SCAN subset scores at 57 months</u>: Prenatal (maternal first trimester) blood Pb : FWS(T): -0.12; FWS(L): -0.11; FWS(R): -0.01; AFGS(T):-0.03; AFGS(L):-0.03; AFGS(R): -0.01; Newborn (10 days) blood Pb: FWS(T): -0.26 p≤0.10**; FWS(L): -0.20 p≤0.01;** FWS(T): -0.13 p≤0.10; AFGS(T): -0.17; AFGS(L) -0.13 p≤0.10; AFGS(R): 0.02 Mean 1st year blood Pb : FWS(T): -0.04; FWS(L): -0.00; FWS(R): -0.06; AFGS(T):-0.08; AFGS(L):-0.05; AFGS(R): -0.03;	Prenatal, neonatal, and postnatal blood Pb was significantly associated with poorer central auditory processing abilities at age 57 months; postnatal blood

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
			Mean 5th year: 11.9 (6.4) Blood Pb measured quarterly to age 5	Kaufman Assessment Battery for Children (K-ABC) at 60 months including a mental processing score (MPC), a simultaneous processing standard score (SIM), a sequential processing standard score (SEQ), a Non-verbal standard score (NONVB), and an achievement standard score (ACHIV)	K-ABC test regression adjustments included head circumference at birth, length at birth, cigarette consumption during pregnancy, social class, preschool attendance, maternal intelligence, HOME scores, and maternal age	Mean 2nd year blood Pb : FWS(T): -0.04; FWS(L): 0.00; FWS(R): -0.06 p≤0.10; AFGS(T):-0.01; AFGS(L):-0.01; AFGS(R): 0.01; Mean 3rd year blood Pb : FWS(T): -0.06; FWS(L): -0.01; **FWS(R): -0.07 p≤0.05;** AFGS(T):-0.01; AFGS(L):-0.02; AFGS(R): 0.02; Mean 4th year blood Pb : FWS(T): -0.07; FWS(L): -0.03; FWS(R): -0.05 p≤0.10; AFGS(T):-0.03; AFGS(L):-0.02; AFGS(R): 0.00; Mean 5th year blood Pb : FWS(T): -0.11 p≤0.10; FWS(L): -0.06 p≤0.10; **FWS(R): -0.08 p≤0.05;** AFGS(T):-0.06; AFGS(L):-0.05; AFGS(R): -0.00; Postnatal (mean lifetime) blood Pb: FWS(T): -0.07; FWS(L): -0.02; **FWS(T): -0.07; p≤0.05** AFGS(T): -0.04; AFGS(L): -0.03; AFGS(R): 0.01; <u>Adjusted regression coefficients for blood Pb indices and 5-year K-ABC scales at 60 months</u>: Prenatal (maternal first trimester) blood Pb : MPC: 0.22; SIM: 0.20; SEQ: 0.15; NONVB: 0.10; ACHIV: 0.10; Newborn (10 days) blood Pb: MPC: -0.10; SIM: -0.17; SEQ: -0.08; NONVB: -0.13; ACHIV: 0.01; Mean 1st year blood Pb : MPC: 0.07; SIM: 0.04; SEQ: 0.12; NONVB: 0.04; ACHIV: 0.12; Mean 2nd year blood Pb : MPC: 0.02; SIM: -0.03; SEQ: 0.04; NONVB: 0.02; ACHIV: 0.04; Mean 3rd year blood Pb : MPC: -0.06; SIM: -0.12; SEQ: -0.00; NONVB: -0.07; ACHIV: -0.03; Mean 4th year blood Pb : MPC: -0.12; **SIM: -0.20 p≤0.05**; SEQ: -0.05; NONVB: -0.15 p≤0.10; ACHIV: -0.05; Mean 5th year blood Pb : MPC: -0.13; SIM: -0.20 p≤0.10; SEQ: -0.07; NONVB: -0.15; ACHIV: -0.11; Postnatal (mean lifetime) blood Pb: MPC: -0.06; SIM: -0.13;SEQ: 0.00; NONVB: -0.08; ACHIV: -0.01;	Pb was significantly associated with poorer performance on cognitive development tests at age 60 months; however adjustment for HOME score and maternal IQ weakened the associations and few remained statistically significant.
Prospective Dietrich (1993b) Cincinnati, OH,	253 children follow-up in the Cincinnati Lead Study;	Followed up at 78 (2) months (=6.5 years)	Prenatal (maternal first trimester): 8.3 (3.7)	Full Scale IQ, Performance IQ, and Verbal IQ as assessed	Multiple linear regression with backward and forward	<u>Adjusted regression coefficients for blood Pb and WISC-R scores</u>: FSIQ; PIQ; VIQ *β* (SE) Prenatal: 0.15 (0.21); 0.06 (0.23); 0.16 (0.21);	Postnatal and average lifetime blood

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
USA *Population may overlap with Dietrich (1987) and others*	Year=births between 1979-1984 % male not stated		Newborn (10 days): 5.0 (3.4) Mean 1st year: 10.6 (5.1) Mean 2nd year: 17.1 (8.4) Mean 3rd year: 16.3 (7.7) Mean 4th year: 14.0 (7.2) Mean 5th year: 11.8 (6.3) Blood Pb measured quarterly to age 5	by the Wechsler Intelligence Scale for Children-Revised (WISC-R) full scale IQ (FSIQ), performance IQ (PIQ) and verbal IQ (VIQ)	elimination procedures HOME score, maternal IQ, birth weight, birth length, child sex, and cigarette consumption during pregnancy	Newborn: -0.03 (0.20); -0.22 (0.22); 0.11 (0.21); 1st year: 0.01 (0.14); -0.16 (0.15); 0.12 (0.14); 2nd year:-0.02 (0.08); -0.10 (0.09); 0.02 (0.08); **3rd year:** -0.13 (0.09); **-0.22 (0.10) p<0.05**; -0.04 (0.09) **4th year:** -0.015 (0.10); **-0.27 (0.11) p<0.05**; -0.02 (0.10); **5th year: -0.23 (0.11) p<0.05; -0.38 (0.12) p<0.05**; -0.07 (0.11); **6th year:-0.33 (0.14) p<0.05; -0.52 (0.15) p<0.001**; -0.12 (0.14); **Mean lifetime:** -0.13 (0.11); **-0.26 (0.12) p<0.05**; -0.01 (0.11); Authors state that average lifetime blood Pb > 20µg/dL was associated with deficits in PIQ on the order of approximately 7 points when compared to children ≤ 10µg/dL.	Pb was significantly with performance and full scale IQ at 6.5 years after adjustments including HOME score and maternal IQ.
Prospective Dietrich (1993a) Cincinnati, OH, USA *Population may overlap with Dietrich (1987) and others*	245 6-year children enrolled in the Cincinnati Lead Study; Year=births between 1979-1984 Male=50.2%;	6 years	Maternal prenatal blood Pb: 8.4 (3.8) Neonatal (10 day) blood Pb: 4.8 (3.1) 6th year blood Pb: 10.1 (5.6)	Comprehensive and standardized assessment of gross- and fine-motor functioning measured by the Bruinsinks-Oseretsky Test of Motor Proficiency (BOTMP); there are eight subtests: running speed and agility, balance, bilateral coordination, strength, upper-limb coordination, response speed, visual-motor control, and upper=limb speed and dexterity	Forward and backward stepwise multiple regression HOME subscales, maternal IQ, social class, and child sex and race	Regression coefficients for blood Pb indices and BOTMP subscales: <u>Prenatal (maternal first trimester) blood Pb :</u> Bilateral coordination: -0.04 (0.08); ns Visual-motor control: 0.06 (0.08); ns Upper-limb speed and dexterity: -0.20 (0.12); ns Fine motor composite: -0.14 (0.21); ns <u>Newborn (10 day) blood Pb:</u> Bilateral coordination: -0.15 (0.09); ≤0.10 Visual-motor control: -0.10 (0.10); ns **Upper-limb speed and dexterity: -0.45 (0.14); p≤0.01** **Fine motor composite: -0.49 (0.24); p≤0.05** <u>Postnatal (mean lifetime) blood Pb:</u> **Bilateral coordination: -0.11 (0.04); p≤0.01** Visual-motor control: -0.05 (0.05); ns **Upper-limb speed and dexterity: -0.19 (0.07); p≤0.01** **Fine motor composite: -0.28 (0.12); p≤0.05** <u>Current blood Pb:</u> **Bilateral coordination: -0.18 (0.04); p≤0.01** **Visual-motor control: -0.12 (0.05); p≤0.05** **Upper-limb speed and dexterity: -0.31 (0.07); p≤0.01** **Fine motor composite: -0.46 (0.13); p≤0.01**	Blood Pb at 10 days, age 6 years, and mean lifetime blood Pb was significantly associated with several measures of gross and fine-motor functions, but maternal first trimester blood Pb was not.
Prospective Dietrich (2001) Cincinnati, OH, USA *Population may overlap with*	195 urban, inner-city adolescents from the Cincinnati Lead Study (CLS); Years=1997-1999; Male=53%	15.6 (0.8) 15-17 years	Maternal prenatal= 8.9 (3.9) (measured in 1st trimester) [Mean levels by category of average exposure presented	Self-Report of Delinquent Behavior and the Parental Report of Predelinquent and Delinquent Behavior (PRDB) in	Backward elimination and forward inclusion step-wise multiple regression Adjusted for birth weight, mean HOME	<u>Association of blood Pb and Self-Report of Delinquent Behavior at age 15 to 17</u>: β (SE) **Maternal prenatal Pb: β = 0.192 (0.76), p=0.002** **78 months Pb: β = 0.193 (0.061), p=0.002** **Avg Childhood Pb: β = 0.101(0.47), p=0.036** <u>Association of blood Pb and Parental Report of</u>	Maternal prenatal, 78 month, and average childhood blood Pb were significantly

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Dietrich (1987) and others			as a figure (under 10µg/dL at birth, peaking between 18 and 21 month, then decreasing.] Adolescents:2.8 (1.3) Blood Pb measured prenatally (maternal), neonatally (10 days), quarterly to age 5, then at 5.5, 6, and 6.5 years and as adolescents.	adolescence; marijuana use also measured	score, parental IQ and current SES	Predelinquent and Delinquent Behavior at 15-17: β (SE) **Maternal prenatal PbB: β (SE)= 0.194 (0.89), p=0.032** 78 months PbB: β (SE)= 0.131 (0.72), p=0.70 Avg Childhood PbB: β (SE)= 0.090 (0.056), p=0.109 Subjects in the highest prenatal Pb category engaged in 2.3 more delinquent acts in the previous 12 months than those in the lowest category. Subjects in the medium and highest average childhood Pb category engaged in approximately 1.5 more delinquent acts than those in the lower category. Subjects in the highest 78 month Pb category engaged in 4.5 more delinquent acts than those in the lowest category Alcohol and marijuana use were independently associated with delinquent behavior as well. Marijuana was correlated with average childhood Pb: *r* = 0.27, ***P*≤0.05**	associated with an increase in self-reported delinquent behavior at age 15-17; maternal prenatal blood Pb was associated with parental reports of delinquent behavior at 15 to 17.

Prospective Emory (2003) Atlanta, GA, USA	79 urban low-socioeconomic status African-American infants – participants of an ongoing study of Pb exposure;
	Year=2000
	% male not stated
		7 months at assessment	Mean maternal blood Pb:
			0.72 (0.86) µg/dL
			Range 0.05-3.3
			
			Maternal exposure measured around 6-7 months gestation and at delivery
				Cognition in the 7-month-old infants was measured by novelty scores from the Fagan test for Infant Intelligence (FTII)	Chi squared.
					
					covariates not reported
						Mean (SD) maternal blood Pb for FTII novelty score catagories:
						Low Risk (>54.5, n=58): 0.65 (0.80) µg/dL
						Medium Risk (53.1-54.5, n=14): 0.89 (0.88) µg/dL
						High Risk (<53.1, n=7): 1.01 (1.26) µg/dL
						Mean maternal blood Pb level (µg/dL) by FTII percentiles: mean (SD)
						5th percentile: 1.18 (0.74)
						15th percentile: 0.94 (0.26)
						85th percentile: 0.44 (0.15)
						95th percentile: 0.28 (0.34)
						Observed (Expect.) number of subjects by 5th (Low) and 95th (High) percentiles of FTII and maternal blood Pb:
						Low FTII: Low Pb = 0 (2.5); High Pb = 5 (2.5);
						High FTII: Low Pb = 5 (2.5); High Pb = 0 (2.5);
						Chi-squared= 10.00; df = 1; p<0.004
						Observed number of subjects by 15th (low) and 85th (high) percentiles of FTII and maternal blood Pb:
						low FTII: low Pb = 7 (9.5); high Pb = 5 (2.5);
						high FTII: low Pb = 12 (9.5); high Pb = 0 (2.5);
						Chi-squared= 12.33; df = 1; p<0.001
							Maternal prenatal blood Pb levels were significantly associated with lower infant intelligence scores.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Ernhart (1986) Cleveland, OH, USA *Population may overlap with Ernhart (1987) and others*	359 infants whose mothers were recruited on their first antenatal visit to clinics that serve the indigent population of Cleveland, OH; 132 mother-infant pairs for whom both maternal and cord blood Pb data was available Year not stated % male not stated	At birth	Cord (N=162) 5.84 (2.02) Maternal (N=185) 6.48 (1.88)	Apgar assessments; Ballard Assessment of Gestational Age; The Brazelton Neonatal Behavioral Assessment Scale (NBAS); the Graham/Rosenblith Behavioral Examination of the Neonate; and examination for Fetal Alcohol Syndrome and general anomalies	Multiple regression analyses; paired maternal and cord analysis Maternal drinking, maternal smoking in pregnancy	Increments in variance of size, Apgar, and Anomalies Tallies, Pb effect variance: <u>Maternal</u> Head circumference= 0.001; ns Apgar, 1 min= 0.009; ns Apgar, 5 min=0.001; ns Fetal Alcohol Syndrome anomalies=0.005; ns General anomalies= 0.006; ns <u>Cord</u> Head circumference= 0.001; ns Apgar, 1 min= 0.001; ns Apgar, 5 min=0.00; ns Fetal Alcohol Syndrome anomalies=0.005; ns General anomalies= 0.00; ns Increment in variance of neurobehavioral tests, Pb effect variance: <u>Maternal</u> Brazelton Test: Habituation= 0.001; ns Orientation= 0.00; ns Motor performance= 0.002; ns Range of state=0.010; ns Regulation of state=0.001; ns Autonomic regulation=0.001; ns Abnormal reflexes=0.002; ns Graham/Rosenblith Test: General maturation= 0.001; ns Soft signs score= 0.004; ns **Muscle Tonus= 0.024; p=0.035** <u>Cord</u> Brazelton Test: Habituation= 0.00; ns Orientation= 0.004; ns Motor performance= 0.001; ns Range of state=0.00; ns Regulation of state=0.001; ns Autonomic regulation=0.003; ns **Abnormal reflexes=0.033; p=0.023** Graham/Rosenblith Test: General maturation= 0.001; ns **Soft signs score= 0.038; p=0.016** Muscle Tonus= 0.001; ns Increments in variance for 132 paired maternal and	Maternal blood Pb was significantly related to the Muscle Tonus Scale and cord blood Pb was significantly related to the Abnormal Reflexes Scale and the Neurological Soft Sign Scale. In paired maternal and cord blood Pb analysis, the significant association of cord blood Pb and Soft Sign Scale remained.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						cord blood Pb exposure indices <u>Maternal</u> Brazelton Abnormal reflexes=0.001; p=0.717 Graham/Rosenblith Neuro, soft signs= 0.007; p=0.354 Muscle tonus=0.016; p=0.153 <u>Cord</u> Brazelton Abnormal reflexes=0.006; p=0.373 Graham/Rosenblith **Neuro, soft signs= 0.056; p=0.008** Muscle tonus=0.015; p=0.162	
Prospective Ernhart (1987) Cleveland, OH, USA *Population may overlap with Ernhart (1986) and others*	119-145 children whose mothers were recruited on their first antenatal visit to clinics that serve the indigent population of Cleveland, OH; Year not stated Male=51%;	6 months ; 1, 2, and 3 years	Maternal (at delivery): 6.5 (1.8) Cord: 5.99(2.11) Maternal exposure measured at delivery; Exposure measured at birth (cord)	Bayley Mental Development Index (MDI) and Psychomotor Development Index (PDI), and modified Kent Infant Development (KID) scale at 6 months; Bayley MDI at 1 year and 2 years; Stanford-Binet Intelligence scale at 3 years	Multiple regression analyses Age, sex, race, birth weight, birth order, gestational exposure to other toxic substances, maternal intelligence, and several indicators of the quality of the caretaking environment, gestational exposure to alcohol and other toxic substances	<u>Maternal and cord blood Pb with developmental outcomes by incremental regression model</u> (variance): Maternal **6 month MDI: 0.0302; p<0.05** **6 month PDI: 0.0295; p<0.05** **6 month KID: 0.0779; p=0.002** 1 year MDI: 0.0002; p=ns 2 year MDI: 0.0020; p=ns 3 year S-B IQ: 0.0059; p=ns Cord 6 month MDI: 0.0046; p=ns 6 month PDI: 0.0006; p=ns 6 month KID: 0.0107; p=ns 1 year MDI: 0.0146; p=ns 2 year MDI: 0.0003; p=ns 3 year S-B IQ: 0.0125; p=ns Correlation between maternal and cord blood Pb= 0.79	Maternal blood Pb at delivery was significantly associated with MDI,PDI, and KID at six months but not at 1, 2, or 3 years, while cord blood Pb was not associated at any age.
Prospective Ernhart (1988) Cleveland, OH, USA *Population may overlap with Ernhart (1986) and others*	131-167 children whose mothers were recruited on their first antenatal visit to clinics that serve the indigent population of Year not stated % male not stated	6 months, 2 years, and 3 years	6 months: 10.05 (3.28) 2 years: 16.74 (6.50) 3 years: 16.95 (6.49)	Bayley Mental Development Index (MDI) at 6 months, 1 year, and 2 years and Psychomotor Development Index (PDI) at 6 months; Stanford-Binet Intelligence scale at 3 years	Incremental regression model Age at testing, race, sex, birth order, parent education, and 2 maternal tests: the intelligence measure PPVT-R, and Authoritarian Family Ideology (AFI); HOME included at ages 1, 2, and 3 years	Relationship of prior and current blood Pb levels with preschool Bayley MDI, PDI and Stanford-Binet measures of development status by incremental regression model (variance): <u>6 month Blood Pb</u> *6 month MDI:0.01; p=0.31 *6 month PDI:0.01; p=0.32 1 year MDI: 0.01; p=0.25 2 year MDI: 0.00; p=0.95 3 year S-B-IQ: 0.00; p=0.49 <u>2 years Blood Pb</u> 2 year MDI: 0.00; p=0.95 3 year S-B IQ:0.01; p=0.29 <u>3 years Blood Pb</u>	Blood Pb at 0.5, 2, and 3 years was not associated with and concurrent or subsequent development index or IQ scale.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						3 year S-B-IQ: 0.00; p=0.98 *does not include HOME in statistical adjustments	
Prospective Ernhart (1989) Cleveland, OH, USA Population may *overlap with Ernhart (1986) and others*	118-135 children whose mothers were recruited on their first antenatal visit to clinics that serve the indigent population of Cleveland, OH; Year not stated Male=51%;	58.3 (0.4) months	Maternal at delivery: 6.5(1.84) Cord: 5.89(2.10)	Cognitive development as assessed by the Wechsler Preschool and Primary Scale of Intelligence (WPPSI)	Linear regression Sex, race, birth order, birth weight, gestational age at birth, parental education, maternal scores (PPVT-R, AFI, AA/day, Cigs/day, Marijuana, other illicit drugs), HOME Score, Medical Problems, Psychosocial problems	Relationship of cord blood Pb level with WPPSI Scores by incremental regression model: Covariate variance (variance): <u>Maternal (N=135)</u> Full Scale IQ: 0.3746 (0.0008) Verbal IQ: 0.3192 (0.0019) Performance IQ: 0.3603 (0.0026) <u>Cord (N=118)</u> Full Scale IQ: 0.4455 (0.0008) Verbal IQ: 0.3615 (0.0019) Performance IQ: 0.4769 (0.0034)	Cord blood Pb and maternal blood Pb were not significantly associated with full scale or subscale IQ scores.
Prospective Ernhart (1990) Cleveland, OH, USA *Population may overlap with Ernhart (1986) and others*	165 children whose mothers were recruited on their first antenatal visit to clinics that serve the indigent population of Cleveland, OH; Year not stated Male=52%;	4.8 years	<u>Maternal at delivery:</u> Arthim.6.56 (1.81) Geom. 6.3 (1.33) <u>Cord:</u> Arthim. 6.03(2.12) Geom. 5.7 (1.41) <u>6 months:</u> Arthim. 10.05 (3.36) Geom.9.57 (1.36) <u>2 year:</u> Arthim.16.74 (6.50) Geom.15.64 (1.44) <u>3 years:</u> Arthim. 16.68 (5.93) Geom. 15.72 (1.41)	Language and Speech Development using the Sequenced Inventory of Communication Development Expressive and Receptive scores at ages 1, 2, and 3 and Speech Production at age 2 measuring Mean Length of Utterances, Intelligibility, and Spontaneity. Other test batteries included the Bayley MDI Scale at 6 months, 1, and 2 years; Stanford-Binet at 3 years; and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) at 4 years, 10 months.	Multivariate regression analyses PPVT-R (maternal IQ estimate), race, sex, maternal authoritarianism, parent education, number of older siblings, maternal Michigan Alcoholism Screening Test, maternal average alcohol ounces per day in-pregnancy, cigarettes during pregnancy, prenatal marijuana use, prenatal street drug use, age of child at testing, HOME score, medical problems, and psychosocial stressors	<u>Correlations between language measures and concurrent or prior Pb measures</u>: Pearson; Adj. Partial 1 year Expressive: Maternal (n=145): -0.13; Adj -0.06; Cord (n=127): -0.18 p<0.05; Adj -0.05; 6 month (n=131): -0.08; Adj -0.04; 1 year Receptive: Maternal (n=145): -0.07; Adj +0.03; Cord (n=127): -0.16; Adj -0.06; 6 month (n=131): +0.08; Adj +0.15; 2 year Expressive: Maternal (n=142): -0.12; Adj +0.03 Cord (n=125): -0.07; Adj +0.04; 6 month (n=126): -0.11; Adj -0.12; 2 year (n=165): **-0.16 p<0.05;** Adj -0.03; 2 year Receptive: Maternal (n=142): -0.13; Adj +0.01; Cord (n=125): -0.09; Adj +0.1; 6 month (n=126): -0.04; Adj -0.12; 2 year (n=165): **-0.20 p<0.05;** Adj -0.01; 3 year Expressive: Maternal (n=138): -0.13; Adj +0.07; Cord (n=120): -0.08; Adj -0.06; 6 month (n=126): -0.05; Adj -0.12; 2 year (n=153): **-0.18 p<0.05;** Adj. -0.09; 3 year (n=165): **-0.21 p<0.01;** Adj -0.04; 3 year Receptive: Maternal (n=138): -0.13; Adj +0.04; Cord (n=120): -0.12; Adj -0.09; 6 month (n=126): -0.10; Adj -0.15;	Cord blood Pb was correlated with mean length of utterances at age 2, but all other associations of cognitive function were not associated with blood Pb from any age after adjustment for relative covariates. Authors conclude that this is likely a chance significant finding.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						2 year (n=153): **-0.19 p<0.05;** Adj -0.04; 3 year (n=165): **-0.17 p<0.05;** Adj +0.08; Mean Length of Utterances age 2: Maternal (n=140): -0.11; Adj -0.03; **Cord (n=124): -0.24 p<0.01; Adj -0.21 p<0.05** 6 month (n=124): -0.05; Adj -0.10; 2 year (n=161): -0.18 p<0.05; Adj -0.08; Intelligibility age 2: Maternal (n=140): -0.06; Adj +0.06; Cord (n=124): -0.14; Adj -0.08; 6 month (n=124): -0.09; Adj -0.17; 2 year (n=161): -0.04; Adj +0.04; Spontaneity age 2: Maternal (n=140): +0.05; Adj +0.13; Cord (n=124): -0.03; Adj +0.02; 6 month (n=124): +0.03; Adj +0.02; 2 year (n=161): +0.04; Adj +0.08; Multivariate analysis of 4 sets of language measures and concurrent or prior blood Pb measures with control of cofactors: None of the p values were statistically significant (all p>0.1)	
Prospective Factor-Litvak (1999) Kosovo, Yugoslavia *Population may overlap with Wasserman (1992) and others*	577 children in Kosovo, Yugoslavia followed from birth to age 10-12 years at 6-month intervals Year=born 1985-1986 % male not stated	7 years	Cumulative (4-7 years) : K. Mitrovica 30µg/dL Pristinia 6.3 µg/dL in	Bayley Scales of Infant Development to assess cognitive function in children up to 2 years; Mental Development Index (MDI) at ages 6, 12, 18, and 24 months; McCarthy Scales of Children's Abilities at age 4 years produced the the General Cognitive Index (GCI) which measures Perceptual Performance, Verbal, Quantitative, Memory, and Motor scales); Wechsler Intelligence Scale for Children-III (WISC III) at age 7 years (measures Total IQ,	Log linear regression model HOME score, ethnic group, maternal age, birth weight, maternal Raven's score, maternal education, birth order, sibship size, sex	Regression of measures of cognitive development and cumulative blood Pb: Bayley Scales of Infant Development (2 yrs of age) **MDI: β(95% CI)= -5.3 (-10.1, -0.5)** McCarthy Scales of Children's Abilities (4 yrs of age) **GCI: β(95% CI)=-9.4 (-14.2, -4.6)** **Perceptual Performance: β(95% CI)=-7.1 (-10.2, -3.9)** **Verbal: β(95% CI)= -2.7 (-5.4, -0.1)** **Quantitative: β(95% CI)= -5.9 (-9.6, -2.3)** **Memory: β(95% CI)= -3.2 (-5.8, -0.5)** **Motor: β(95% CI)= -4.3 (-8.3, -0.3)** WISC III (7 years of age) **Full Scale IQ: β(95% CI)= -9.0 (-12.4, -5.5)** **Performance IQ: β(95% CI)= -9.4 (-13.3, -5.6)** **Verbal IQ: β(95% CI)= -7.1 (-10.5, -3.7)**	Cumulative blood Pb is associated with poorer intellectual function at 2, 4, and 7 years.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				Verbal IQ, and Performance IQ)			
Cross Sectional Fergusson (1988b) New Zealand *Population may overlap with Fergusson (1993) and others*	888 children from the Christchurch Child Development Study (later as the Christchurch Health and Development Study) birth cohort (1977); examined at birth, 4 months, and then annually Year=1985-86 % male not stated	mean not reported 8-9 years	Dentine Pb mean not reported 6.2 (3.70) µg/g; measured at ages 6-8 years from Fergusson (1993)	Behavior measured by Rutter and Conners behavior ratings questionnaires	Bivariate correlations Maternal education, birth placement, child's gender, standard of living, avoidance of punishment, change of parents, changes of school, old weatherboard houses, traffic density, age of tooth, tooth position, sample selection hazard	Correlations between true dentine Pb values and inattentive/restless behavior **8 years: r=0.08; p<0.01** **9 years: r=0.08; p<0.01**	Dentine Pb is significantly correlated with inattention/restlessness at ages 8 and 9 years.
Prospective Fergusson (1993) New Zealand *Population may overlap with (Fergusson et al. 1988b) and others*	690-891 children from the Christchurch Health and Development Study birth cohort (1977); examined at birth, 4 months, and then annually. Year=1989-1990 % male not stated	mean not reported 12-13 years	Tooth (dentine) Pb: 6.2 (3.70) µg/g Measured at ages 6-8 years	Behavior, cognition, and educational outcomes at age 12-13 were measured by measures of word recognition using the Burt Word Reading Test, Reading comprehension by the Progressive Achievement Test (PAT), Measures of Scholastic Abilities (TOSCA), Teachers ratings of school performance, and Rutter and Conners f inattention/restlessness by parent teacher questionnaires.	Multiple regression Maternal education, paternal education, family size, gender, socio-economic status, ethnicity, number of school attended, maternal emotional responsiveness, avoidance of punishment, number of years residence in weatherboard housing	<u>Regression of mean test scores at 12-13 years by dentine Pb levels</u> (6-8 years; dose-response): <u>Standardized tests</u> **Burt (12 years): β=-0.07; p<0.05** Burt (13 years): β=-0.05; p=NS **PAT (12 years): β=-0.06; p<0.10** **TOSCA (13 years): -0.07; p<0.05** <u>Teachers ratings</u> Reading **12 years: β=-0.10; p<0.005** **13 years: β=-0.07; p<0.05** Written expression **12 years: β=-0.11; p<0.001** **13 years: β=-0.08; p<0.01** Mathematics **12 years: β=-0.06; p<0.05** **13 years: β=-0.16; p<0.001** Inattention/restlessness **12 years: β=0.11; p<0.001** **13 years: β=0.06; p<0.05**	Tooth Pb levels taken at 6-8 years had a statistically significant dose-response association with standardized tests of achievement and cognition, teachers' ratings and inattention/restlessness at age 12-13
Prospective Fergusson (1997) New Zealand *Population may overlap with (Fergusson et al. 1988b) and others*	1265 children from the Christchurch Health and Development Study birth cohort (1977); examined at birth, 4 months, annually until age 16 years, and at 18 years Year=1983-1995	6-8; 16-18	Dentine Pb levels at 6-8 years (µg g^{-1}) mean not reported 0-2: N= 91 3-5: N=418 6-8: N=241 9-11: N=87 12+: N=44	Cognitive and Educational Outcomes at age 18 assessed by measures of word recognition using the Burt Word Reading Test, number of years of secondary school education,	Multiple linear Burt Reading Test, number of School Certificate subjects passed; Logistic regression for low reading ability, failure to complete 3 years in high school, leaving school without formal educational	Educational outcomes at 16-18 years by dentine Pb level (µg g^{-1}) at 6-8 years: <u>Mean Burt Word Reading Test score (18 years):</u> 0-2 µg g^{-1}: 99.05 3-5 µg g^{-1}: 98.33 6-8 µg g^{-1}: 97.41 9-11 µg g^{-1}: 96.43 12+ µg g^{-1}: 94.08 **p<0.002** <u>% Scoring below 12-year-old average on Burt Test at 18</u>	Dentine Pb at age 6-8 years was significantly associated with poorer cognitive test scores and academic achievement at

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	% male not stated			mean number of School Certificate passes, and leaving school without formal qualifications	qualifications) Gender, maternal age, maternal education, socioeconomic status, standard of living, duration of breastfeeding, birth order, parental conflict, maternal punitiveness, class level, years lived near busy roads	years: 0-2 µg g^{-1}: 5.3 3-5 µg g^{-1}: 6.3 6-8 µg g^{-1}: 7.8 9-11 µg g^{-1}: 9.7 12+ µg g^{-1}: 16.5 **p<0.001** % Failing to complete 3 years of secondary school 0-2 µg g^{-1}: 6.1 3-5 µg g^{-1}: 6.8 6-8 µg g^{-1}: 7.8 9-11 µg g^{-1}: 9.1 12+ µg g^{-1}: 13.1 **p<0.02** % Leaving school with no qualifications 0-2 µg g^{-1}: 15.6 3-5 µg g^{-1}: 16.7 6-8 µg g^{-1}: 18.1 9-11 µg g^{-1}: 19.7 12+ µg g^{-1}: 24.1 **p<0.05** Mean number of School Certificate passes (C grade or better) 0-2 µg g^{-1}: 3.52 3-5 µg g^{-1}: 3.45 6-8 µg g^{-1}: 3.37 9-11 µg g^{-1}: 3.27 12+ µg g^{-1}: 3.06 **p<0.05**	age 18.
Prospective Fergusson (2008) New Zealand *Population may overlap with (Fergusson et al. 1988b) and others*	1265 children from the Christchurch Health and Development Study birth cohort (1977); examined at birth, 4 months, and then annually or bi annually Year=1991-1998 Male= 51 %	21 years	[mean levels not stated] Dentine Pb levels 0 – 2 µg/g (n=86) 3 – 5 µg/g (n=409) 6 – 8 µg/g (n=231); 9 – 11 µg/g (n=83); 12+ µg/g (n=44) Exposure measured in deciduous teeth collected at age 6-8	History of criminal behavior was based on police records and self-reported offenses.	Negative binomial regression models; pseudo-R^2 statistics Officially reported crime: family socioeconomic status at birth, ethnicity, parental criminal offending, parental alcoholism; intervening factors: leaving school without qualifications, GPA, ages 11-13 Self-reported crime:	Association between dentine Pb levels and officially reported crime (violent/prop. convictions ages 14-21): **B = 0.49 (0.17); p=0.005** Association between dentine Pb levels and self-reported crime: **B = 0.20 (0.10); p=0.047** Association between dentine Pb levels and officially reported crime (violent/prop. convictions ages 14-21) after adjustment for educational factors: **B = 0.41 (0.18); p=0.02** Association between dentine Pb levels and self-reported crime ages 14-21 after adjustment for educational factors: B = 0.07 (0.11); p=0.52	Dentine Pb levels at ages 6-8 were significantly associated with officially reported and self-reported crime from ages 14-21; association with Pb and self-reported crime was not significant after adjustment for

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
					maternal education level, child ethnicity, family conflict, maternal smoking during pregnancy, exposure to childhood physical abuse, parental alcohol problems, parental criminal offending; intervening factors: leaving school without qualification, grade point average at ages 11 – 13 years.	Authors state associations were largely explained by linkages between Pb exposure and educational underachievement.	educational factors.
Cross-sectional Fishbein (2008) Baltimore, MD USA	26 female injection heroin users, at least 18 years old, hepatitis C positive, premenopausal, not pregnant and living in Baltimore Year not stated Male= 0%	42.5 (5.1) years	Tibia Pb: 14.5 µg/g Current Tibia Pb measurement	Cognitive ability measured by The Cambridge Decision Making Task, The Logan Stop-Change Task, and The Stroop Color Word Interference Task.	Univariate distributions; small scale regression analyses; simple correlation analyses; linear regression models.	Tibia Pb concentrations and cognitive data: Cognitive flexibility: p=NS **Risky decisions: p<0.05** Impulsivity: p=NS Interaction effects of tibia Pb and cognitive functioning on frequency of heroin use: **Tibia Pb by cognitive flexibility** **β = -0.80; p=0.007** **Tibia Pb by risky decisions** **β = 0.75; p=0.007** Tibia Pb by impulsivity β=0.06; p=0.75	Tibia Pb concentrations were significantly associated with risky decision making; interactions of tibia Pb with cognitive inflexibility and risky decision making were significantly related to frequency of heroin use
Prospective Froehlich (2007) Rochester, NY USA *Population may overlap with Canfield (2003b) and others*	176 children in Rochester, NY; Year not stated Male = 51%	Enrolled during infancy; assessed at age 5	At 60 months: 6.1 (4.9) µg/dL	Executive function at 66 months from the Cambridge Neuropsychological Testing Automated Battery: spatial working memory (SWM), rule learning and reversal (RLR), spatial span (SS), and planning (P) *Also genotyped DRD4*	Pearson correlation coefficient; Multivariable linear regression Adjusted for income (SWR); neonatal intensive care unit and sex (RLR); HOME score, maternal IQ, and race (SS Span Length); mom's age at delivery, maternal education,	66 month executive function and 60 month blood Pb: *r*, adj*β* (SE) for all subjects without *DRD4* interaction SWM Total Errors: **0.19*,** 0.51 (0.34) SWM Between-Search Errors: **0.19*,** 0.47 (0.32) **RLR Stages Completed: -0.18*, -0.06 (0.03)**** **RLR Total Trials-Adjusted: 0.18*, 2.56 (1.25)**** **SS Span Length: -0.28*, -0.02 (0.1)**** SS Total Errors: 0.07, 0.04 (0.04) P Problems Solved in Min. Moves: **-0.23*,** -0.06 (0.04) **P Mean Moves-3 Move Problem: 0.24*, 0.08 (0.03)**** **p ≤ 0.01 *p ≤ 0.05	Blood Pb was significantly associated with several measures of impaired executive function at age 5. The effects of *DRD4-7* genotype and Pb on executive function were

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				exon III locus	marital status, and span length (SS Total Errors); maternal IQ and transferrin saturation (P Problems Solved in Min. Moves); and in utero tobacco exposure (P Mean Moves-3 Move Problem)	Boys showed more Pb-related impairment than girls (Pb-sex interaction: P Mean Moves p = 0.0008, P Problems Solved p = 0.049) *DRD4*-7 was associated with poorer spatial working memory and more impaired by increasing Pb for RLR.	independent and Pb effects were modified by DRD4 genotype and gender.
Cross-sectional Froehlich (2009) USA *Population may overlap with Braun (2006)*	2588 children from NHANES 2001-2004 Year=2001-2004 % male not stated	[mean age not stated] Range: 8 – 15 years old.	[blood Pb levels for the entire population were not stated] Current blood Pb level measures	ADHD (diagnosed using the National Institute of Mental Health Diagnostic Interview Schedule for Children; a caregiver's report of a previous ADHD diagnosis was also accepted), and prenatal tobacco A secondary outcome variable was created for children who had been treated with ADHD medication in the past year.	Logistic regression analyses; regression diagnostic analyses. Child gender, household income/poverty line ratio, race/ethnicity, mother's age at child's birth, birth weight, NICU admission, postnatal secondhand tobacco smoke exposure, preschool attendance.	AdjOR for ADHD by blood Pb tertile: 1st tertile (0.2-0.8 µg/dL) = 1.0 (reference) 2nd tertile (0.9-1.3 µg/dL) = 1.7 (0.97, 2.9)(*p*=0.06) **3rd tertile (> 1.3 µg/dL) = 2.3 (1.5, 3.8) (p=0.001)** AdjOR for ADHD by prenatal tobacco (Yes/no): No 1.0 (reference) **Yes = 2.4 (1.5, 3.7) (p=0.001)** AdjOR for ADHD by prenatal tobacco and 3rd tertile blood Pb **(> 1.3 µg/dL)**: **8.1(3.5, 18.7) (p=0.001 tobacco-Pb interaction term)**	Blood Pb levels were positively and significantly associated with ADHD in children aged 8 to 15 with significant interaction with prenatal tobacco exposure
Cross-sectional Fulton (1987) Edinburgh, Scotland *Population may overlap with (Thomson et al. 1989)*	501 children recruited from 18 primary schools in classes 3 and 4 in education authority primary schools in central Edinburgh. Year not stated, began in 1982 Male = 52%	6-9 years	Geometric mean: 10.4	British Ability Scales; behavior ratings by parents and teachers including tests to measure cognitive abilities (sampling, visuospatial, perceptual, short-term memory, and language functions) and educational attainment (number concepts and computational ability, and word reading)	Multiple regression analysis Child: age, sex, handedness, standardized height, birth problems score, length of gestation, birthweight, medical history score, days absent from school; Parents: mother's social class, father's social class, mother's qualifications, father's qualifications, father or single mother)	<u>Log blood Pb coefficients for ability and attainment tests</u>: β (SE) **BAS combined score: -3.79 (1.37); p=0.003** **Numbers score:-1.47 (0.83); p=0.039** **Reading score: -3.16 (1.05); p=0.001**	Concurrent blood Pb was significantly associated with lower British Ability Scales combined score, number skills, and word reading at age 6-9 years.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				All raw scores were transformed to give BAS combed scores.	unemployed, mother (or single father) at work, parents' health score, parents' mental health score, smoking, parent's vocabulary, parent's matrices test; Family: family size, birth order, family structure score, parent/child communication, parental involvement with school, child's interest parental participating with child; School: recent change of school, class year, time of day of tests; Household: people per room, car/telephone ownership, consumer goods ownership; Other: school, Pb		
Cross-sectional Gao (2008) China	188 people from 4 rural provinces in a larger cohort of people over 65; Year 2003-2005 Male = 50%	69.2 (4.1) (statistically significantly younger than the cohort without trace elements measured)	3.91 (6.27) µg/dL Range 0.30-39.34 (n=187, one excluded with 125.2µg/dL) *Table lists units as µg/L, but µg/dL is more consistent with measured values)	Cognitive assessment with the Community Screening Instrument for Dementia (CSID), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Learning and Recall Tests, and the Indiana University Story Recall, Animal Fluency, and Token tests *Also measured Al, Ca, Cd, Cu, Fe, and Zn and genotyped APOE*	Analysis of Covariance Models (ANCOVA) of the composite z Score Adjusted for age, gender, education, BMI, and *APOE ε4* status	ANCOVA for composite z Score and blood Pb: Estimate: -0.009 (SE 0.008), $p = 0.2496$ Other elements were significantly associated (Ca $p < 0.0001$, Cd $p = 0.0044$, Cu $p = 0.0121$).	Concurrent blood Pb was not significantly associated with a composite cognitive function score in adults.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Glass (2009) Baltimore, MD, USA *Population may overlap with Shih (2006) and others*	1,001 older adults in the Baltimore Memory Study; Year=2001-2005 Male = 34.1%	59.4 (6.0) Range: 50-70	Mean tibia Pb at baseline (2001-2003): 18.8 (11.1) µg/g	Cognitive assessment by 20 tests grouped into 7 cognitive domains: language (Boston Naming, letter fluency, and category fluency), processing speed (simple reaction time), eye-hand coordination (Purdue pegboard, Stroop C form minus A form, and trail-making test A), verbal memory and learning (Rey auditory verbal learning test), visual memory (Rey complex figure recall and symbol digit), and visuoconstruction (Rey complex figure copy). All standardized so a negative coefficient indicates worse performance. *Neighborhood psychosocial hazards (NPH) also measured*	Multilevel hierarchical mixed-effects regression models Adjusted for age, sex, race/ethnicity, education, testing technician, and time of day	Adjusted association of tibia Pb, NPH, and their interaction with cognitive function: β (95%CI) Language (n=998) Tibia main effect: 0.004 (-0.002, 0.011) NPH middle vs low: 0.002 (-0.178, 0.181) NPH high vs. low: 0.105 (-0.086, 0.296) Tibia x Middle NPH: 0.001 (-0.008, 0.009) Tibia x High NPH: -0.009 (-0.017, -0.0001), $P < 0.1$ **X^2 test for Interaction (2 df): 6.5, $P = 0.039$** Processing Speed (n=999) Tibia main effect: 0.007 (-0.001, 0.015) NPH middle vs low: 0.141 (-0.084, 0.366) NPH high vs. low:0.038 (-0.200, 0.276) Tibia x Middle NPH: -0.012 (-0.022, -0.001), $P < 0.1$ Tibia x High NPH: -0.011 (-0.022, -0.0001), $P < 0.1$ X^2 test for Interaction (2 df): 5.4, $P = 0.067$ Eye-Hand Coordination (n=997) Tibia main effect: 0.002 (-0.004, 0.01) NPH middle vs low: 0.016 (-0.163, 0.20) NPH high vs. low: -0.047 (-0.237, 0.14) Tibia x Middle NPH: -0.004 (-0.012, 0.005) Tibia x High NPH: -0.006 (-0.015, 0.002) X^2 test for Interaction (2 df): 2.0, $P = 0.368$ Executive Functioning (n=996) Tibia main effect: 0.004 (-0.003, 0.01) NPH middle vs low: -0.038 (-0.205, 0.13) NPH high vs. low: 0.058 (-0.118, 0.232) Tibia x Middle NPH: -0.002 (-0.010, 0.006) **Tibia x High NPH: -0.010 (-0.018, -0.002), $P < 0.05$** **X^2 test for Interaction (2 df): 7.4, $P = 0.025$** Verbal Learning and Memory (n=997) Tibia main effect: 0.001 (-0.006, 0.01) NPH middle vs low: 0.164 (-0.055, 0.38) NPH high vs. low: 0.118 (-0.115, 0.35) Tibia x Middle NPH: -0.007 (-0.017, 0.004) Tibia x High NPH: -0.006 (-0.016, 0.005) X^2 test for Interaction (2 df): 1.8, $P = 0.407$ Visual Memory (n=997) Tibia main effect: 0.001 (-0.007, 0.01) NPH middle vs low: 0.016 (-0.210, 0.24) NPH high vs. low: 0.061 (-0.180, 0.30) Tibia x Middle NPH: 0.001 (-0.010, 0.011) Tibia x High NPH: -0.007 (-0.018, 0.004) X^2 test for Interaction (2 df): 2.9, $P = 0.235$ Visuoconstruction (n=1,000)	Tibia Pb and high neighborhood psychosocial hazards were significantly associated with impaired executive functioning, with a significant interaction for executive functioning and language scores.

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						Tibia main effect: 0.000 (-0.009, 0.01) NPH middle vs low: 0.149 (-0.089, 0.39) NPH high vs. low: 0.014 (-0.238, 0.27) Tibia x Middle NPH: -0.003 (-0.014, 0.008) Tibia x High NPH: -0.006 (-0.017, 0.005) X^2 test for Interaction (2 df): 1.0, *P* = 0.607	
Cross-sectional Golub (2009) USA	4159 adults (aged 20 and over) from NHANES 2005-6 Year = 2005-2006 Male=48%	46.50 years	1.75 µg/dL	Depression evaluated using the CDC's Patient Health Questionnaire (PHQ-9)	Relative risks were calculated using Poisson regression; odds ratios were calculated with ordinal logistic regression Age, sex, education level, ethnicity, and poverty income ratio.	Blood Pb in relation to depression prevalence (Poisson regression): Continuous Pb, RR = 1.01 (0.96, 1.07) Categorical Pb 0 – 0.88 µg/dL, RR = 1.00 (reference) 0.89 – 1.40 µg/dL, RR = 1.16 (0.99, 1.36) **1.41 – 2.17 µg/dL, RR = 1.20 (1.07, 1.36)** 2.18 – 26.4 µg/dL, RR = 1.16 (0.87, 1.54) Blood Pb in relation to depression prevalence (ordinal logistic regression): Continuous Pb, RR = 1.01 (0.94, 1.09) Categorical Pb 0 – 0.88 µg/dL, RR = 1.00 (reference) 0.89 – 1.40 µg/dL, RR = 1.22 (0.98, 1.51) **1.41 – 2.17 µg/dL, RR = 1.25 (1.07, 1.47)** 2.18 – 26.4 µg/dL, RR = 1.18 (0.83, 1.68)	Blood Pb levels were significantly associated with a higher risk of patient reported depression.
Prospective Gomaa (2002) Mexico City, Mexico *Population may overlap with Hu (2006) and others*	197 mother-infant pairs from the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) sequential birth cohort recruited from 3 low to moderate income hospitals; Year: 1994–1995 Male=54%	24 months	Infant blood Pb: Cord =6.7 (3.4) 12 mo.=7.2(2.8) 24 mo.=8.4(4.6) Maternal (1 month after delivery) Tibia bone: =11.5 (11.0)µg/g Trabecular bone: = 17.9 (5.2)µg/g	Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores as assessed using the Bayley Scales of Infant Development II (BSID-II; Spanish version)	Bivariate analysis and multiple linear regression using forward, backward, and stepwise methods Maternal age, IQ, and education; paternal education; marital status; breastfeeding duration; infant gender; and infant illness	Linear regression of MDI to cord blood Pb or maternal bone Pb β(SE): **Cord blood Pb β= -4.94(2.07); p=0.0179** **Maternal patellar Pb β=-0.16(0.07); p=0.03** 2nd quartile patellar Pb β=-5.25(2.81); p=0.06 **3rd quartile patellar Pb β=-7.66(2.85); p=0.01** **4th quartile patellar Pb β=-7.20(2.88); p=0.01** Maternal tibia Pb β=-0.10(0.10); p=0.30 Cord and patellar combined model Cord blood Pb β= -4.21(2.09); p=0.05 Maternal patellar Pb β=-0.13(0.07); p=0.07 2nd quartile patellar Pb β=-5.05(2.78); p=0.07 **3rd quartile patellar Pb β=-7.32(2.83); p=0.01** **4th quartile patellar Pb β=-6.33(2.88); p=0.03**	Cord blood Pb and maternal patella Pb one month after delivery were significantly associated with the decreased MDI scores but maternal tibia Pb was not.
Prospective Gump (2008) Oswego, NY, USA *Population may overlap with Gump (2009)*	154 children enrolled in the Oswego Children's Study; Year not stated Male=46% (of original 169 participants)	9.5 (0.04)	Range Cord: <1.0 - 6.3 Postnatal (mean age 2.6):1.5-13.1 Quartiles Cord: ≤1.0, 1.1-1.4, 1.5-2.0, 2.1-4.4 Postnatal (mean age	Adrenocortical responses to an acute stressor measured using assays of salivary cortisol before and after standard cold pressor task	Regression (Pb as continuous variable); Test of linear contrast across Pb quartiles Demographics, health/nutrition, infant/birth	Test of linear contrast across quartiles: Initial salivary cortisol: Pre and postnatal Pb exposure p>0.05 Cortisol response to acute stress at 9.5 year of age: **Prenatal Pb –** **cortisol responses p<0.001** **p<0.0001 after adjustment for postnatal Pb** **Postnatal Pb –**	Cord and early childhood blood Pb was significantly associated with increased cortisol response to

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
			2.6):1.5-2.8, 2.9-4.1, 4.2-5.4, 5.5-13.1		characteristics/substance use	**cortisol responses p<0.005** **p<0.05 after adjustment for prenatal Pb** <u>Regression of cortisol reactivity and blood Pb:</u> Prenatal: **21 min (p<0.005); 40 min (p<0.01); 60 min (p<0.05)** Postnatal Pb: **21 min (p<0.05);** 40 min (p<0.10); **60 min (p<0.05)**	acute stress at age 9.5 years.
Prospective Gump (2009) Oswego, NY, USA *Population may overlap with Gump (2008)*	108 children from the Oswego Children's Study; Year not stated % male not stated	9.5	Early childhood (mean age 2.3 years): Range = 1.5 to 13.10 µg/dL	Adrenocortical responses to an acute stressor measured using assays of salivary cortisol before and after standard cold pressor task, mirror tracing task and reaction time	A series of regression analyses Adjustments differ by time point including mother's age, father's age, HOME score, birth weight, head circumference, maternal coffee consumption and other factors	Association between Socioeconomic Status (SES) and cortisol following acute stress, then controlling for blood Pb, and sobel test: Cortisol (full model) **SES→cortisol 4.04; p<0.05** SES(+Pb)→ 1.51; p>0.05**; Sobel test z=2.04; p<0.05** Change at 21 min **SES→cortisol 4.46; p<0.05** SES(+Pb)→ 1.44; p>0.05; Sobel test z=1.64; p<0.1 Change at 40 min SES→cortisol 2.89; p<0.1 SES(+Pb)→ 1.08; p>0.05; Sobel test z=1.50; p>0.05 Change at 60 min SES→cortisol 2.37; p>0.05 **SES(+Pb)→ 0.76; p>0.05; Sobel test z=1.90; p<0.05** Authors state blood Pb was a significant mediator of SES effect on cortisol response to acute stress in full model and at 60 minutes.	Childhood blood Pb was a significant mediator of the association between socioeconomic status and heightened adrenocortical responses to acute stressors at age 9.5 years.
Cross-sectional Groenewold (2007) Louisville, KY, USA	2011 children enrolled in the 3rd grade from Jefferson County Public Schools, Louisville Metro Health Department Year=2003 Male= 47.8%	3rd grade (usually age 8-9)	Mean peak blood Pb: 7.17 (5.01)	Comprehensive Test of Basic Skills (CTBS) portion of the Commonwealth Accountability Testing System	Multiple regression Sex, race, missing race effect, school attendance, individual and area-based SES	Regression of decrements in CTBS scores per 1 µg/dL increase in blood Pb level: β(95% CI) **Total Battery: -0.430 (-0.599, -0.261); p<0.001** **Reading: -0.426 (-0.600, -0.253); p<0.001** **Math: -0.324 (-0.497, -0.151); p<0.001** **Language: -0.435 (-0.600, -0.270); p=0.037**	Blood Pb levels are significantly associated with decreased CTBS scores in the third grade (usually age 8-9).
Cross-sectional Ha (2009) Korea	1778 children in the Children's Health and Environment Research study (CHEER) in South Korea; Year=recruited in 2005 Male=52%	7.1(0.8)	Geometric mean =1.8(1.71) Measured when outcome assessed	ADHD evaluated using abbreviated Conners' scale for ADHD screening (Korean version), blood Hg	Logistic regression Age, gender, household income, parental history of neuropsychiatric disease, and residential area	Multivariate regression of blood Pb and Conners' ADHD score for each 1µg/dL blood Pb: **β= 0.50, p < 0.0001** ADHD symptoms in children with blood Pb: OR (95% CI) <1.0 µg/dL -reference 1-<1.5µg/dL Adj.OR= 1.28 (0.57, 2.86) <2.5 µg/dL Adj.OR= 1.32 (0.63, 2.74) <3.5 µg/dL Adj.OR= 1.65 (0.77, 3.56) >3.5 µg/dL Adj.OR= 1.98 (0.76, 5.13); p- trend =0.07 Blood mercury was not associated with ADHD.	Blood Pb was significantly associated with ADHD screening score, but not specific ADHD symptoms in elementary school children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Hornung (2009) Cincinnati, OH and Rochester NY, USA *Population may overlap with Canfield (2003b) and others*	221 children enrolled in the Cincinnati Pb Study during 1979-1984 and 176 children enrolled in the Rochester Longitudinal Study Year= 1994-1995 Male=51%	6 years	Geometric mean (5^{th} – 95^{th} percentile) Lifetime: 8.5 (3.0-22.1) Peak: 13.6 (4.6-34.4) Early Childhood: 8.9 (3.0-23.8) Concurrent: 6.0 (1.9-17.9) Measured yearly from 1-6 years of age	Cognitive development evaluated using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and the Wechsler Intelligence Scale for Children revised (WISC-R)	Multiple regression models Site, average childhood blood Pb, HOME score, birth weight, maternal IQ, maternal education level.	Log-linear relationship between IQ at age 6 and blood Pb level at various ages β (SE): 1 year, β = -0.08 (1.02); *p*=0.934 2 years, β = -0.46 (1.08); *p*=0.670 **3 years, β = -2.61 (1.05); *p*=0.013** **4 years, β = -2.85 (1.07); *p*=0.008** **5 years, β = -4.39 (0.95); *p*<0.001** **6 years, β = -3.49 (1.03); *p*<0.001** Final model for blood Pb and log-linear relationship with age 6 IQ: **6 to 2 year Ratio β = -7.00 (1.54); p<0.001** **Avg. childhood blood Pb β = -3.19 (1.23); *p*=0.010**	Average childhood blood Pb and blood Pb at ages 3, 4, 5, and 6 were significantly associated with lower IQ at age 6.
Case-control Hsieh (2009) Taiwan	22 workers in a Pb paint factory and 18 factory workers that did not use Pb; Year not stated Male = 72-77%	Referents = 46.0 (10.14) years Pb exposed = 45.7 (11.72) years	Blood Referents=3.4(1.1) Pb=16.99 (10.38) Tibia (µg/g) Referent=18.5 (22.4) Pb=61.55 (30.21) Patella (µg/g) Referent=7.14 (9.81) Pb=66.29 (19.48)	Magnetic resonance spectroscopy (MRS) imaging data, brain N-acetyl aspartate (NAA), choline (Cho), and total creatinine (tCr)	*t*-tests, chi-square and Fisher exact tests; multiple linear regressions using standardized regression coefficients. Sex, age, smoking status, alcohol use, work duration, BMI, and betel nut chewing.	Regression coefficients of human brain Cho:tCr ratios with Pb: Frontal lobe gray matter **Blood, β = -0.014 (0.005) (*p*<0.05)** **Patella, β = -0.004 (0.001) (*p*<0.05)** **Tibia, β = -0.004 (0.001) (*p*<0.05)** Occipital lobe gray matter **Blood, β = -0.016 (0.005) (*p*<0.05)** **Patella, β = -0.004 (0.001) (*p*<0.05)** **Tibia, β = -0.004 (0.001) (*p*<0.05)** Occipital lobe subcortical white matter **Blood, β = -0.018 (0.007) (*p*<0.05)** **Patella, β = -0.006 (0.002) (*p*<0.05)** **Tibia, β = -0.004 (0.002) (*p*<0.05)** Occipital lobe white matter **Blood, β = -0.018 (0.007) (*p*<0.05)** **Patella, β = -0.006 (0.002) (*p*<0.05)** **Tibia, β = -0.004 (0.002) (*p*<0.05)** Regression coefficients of human brain NAA:tCr ratios with Pb: Frontal lobe gray matter **Blood, β = -0.023 (0.005) (*p*<0.05)** **Patella, β = -0.004 (0.001) (*p*<0.05)** **Tibia, β = -0.003 (0.001) (*p*<0.05)** Frontal lobe subcortical white matter **Blood, β = -0.011 (0.005) (*p*<0.05)** **Patella, β = -0.003 (0.001) (*p*<0.05)** Tibia, β = -0.004 (0.001) Frontal lobe white matter **Blood, β = -0.015 (0.006) (*p*<0.05)** **Patella, β = -0.004 (0.002) (*p*<0.05)** Tibia, β = -0.001 (0.002) Occipital lobe white matter	Blood and bone Pb levels were significantly associated with altered brain metabolism (decreased NAA:tCr and Cho:tCr ratios) in adults.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Blood, β = -0.018 (0.007) (*p*<0.05) **Patella, β = -0.006 (0.002) (*p*<0.05)** **Tibia, β = -0.005 (0.002) (*p*<0.05)**	
Prospective Hu (2006) Mexico City, Mexico *Population may overlap with Gomaa (2002) and others*	146 infant-mother pairs from the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) sequential birth cohort recruited from 3 low to moderate income hospitals; Year=1997-1999 Male children=76%	24 months Maternal age: 27.1 (5.3)	Whole Blood Pb: 1st tri.= 7.1(5.1) 2nd tri. = 6.1 (3.2) 3rd tri. = 6.9 (4.2) Delivery = 7.3 (4.3) Plasma Pb **(µg/L)**: 1st tri.= 0.16 (0.14) 2nd tri. = 0.14 (0.11) 3rd tri. = 0.16 (0.24) Child blood Pb: Cord = 6.2 (3.9) 12 mon = 5.22 (3.41) 24 mon = 4.79 (3.71)	Bayley Scales of Infant Development Mental Development Index (MDI) at 24 months	Multivariate linear regression Adjusted for infant's concurrent blood Pb (24 months of age), sex, maternal age, current weight, height-for-age Z-score, and maternal IQ	Adjusted single-trimester regression for MDI at 24 months and logPb exposure: β (95% CI); *p*-value Blood Pb in Pregnancy: **1st trimester: -4.13 (-8.10, -0.17); p=0.04** **2nd trimester: -4.08 (-8.29, 0.12); p=0.06** 3rd trimester: -2.42 (06.38, 1.54); p=0.23 Average: -3.52 (-7.66, 0.63); p=0.10 Plasma Pb in Pregnancy: **1st trimester: -3.77 (-7.12, -0.42); p=0.03** 2nd trimester: -2.48 (-5.74, 0.77); p=0.13 3rd trimester: -0.32 (-3.38, 2.74); p=0.83 Average: -3.11 (-6.53, 0.31); p=0.07 Child blood Pb: Cord: -0.35 (-4.7, 4.03) 12 month: -2.38 (-6.24, 1.49); p= 0.23 24 month: -1.00 (-3.93, 1.94); p=0.50 Multivariate model of MDI at 24 months and maternal Pb during pregnancy: *β*; *p*-value Plasma model (R^2 = 0.22) **1st trimester: *β* = -3.54; p = 0.03** 2nd trimester: *β* = 0.80; p = 0.65 3rd trimester: *β* = 1.18; p = 0.44 24 month blood Pb: *β* = -0.01; p = 0.62 Blood model (R^2 = 0.21) 1st trimester: *β* = -2.40; p = 0.19 2nd trimester: *β* = -1.29; p = 0.56 3rd trimester: *β* = 1.42; p = 0.46 24 month blood Pb: *β* = -0.01; p =0.80	Maternal blood Pb in 1st trimester was significantly associated with lower MDI scores in their children at age 24 months.
Cross-sectional Hubbs-Tait (2007) OK, USA *Population may overlap with Hubbs-Tait (2009)*	42 children 3-5 years old, attending rural Head Start centers in northern Oklahoma. Year= 2006; % male not stated	4.92 (0.59)	1.86 (1.24, 2.90)	Teachers rated children's behavior on the California Preschool Social Competency Scale, Howes' Sociability subscale, and the Preschool Behavior Questionnaire; McCarthy Scales of Children's Abilities	Hierarchical regression analyses	McCarthy Scales of Children's Ability Verbal Score β=-0.14 ; p=0.33 McCarthy Scales of Children's Ability Perceptual Score β=-0.13; p=0.41 California Preschool Social Competency (girls) **β= -0.60; p=0.02** Sociable (girls) **β=-0.67; p=0.01** Preschool Behavior Questionnaire Anxious (boys) β= 0.17; p=0.46	Concurrent blood Pb was significantly associated with lower teacher ratings of girls' sociability and classroom social competence at age 3-5 years.
Cross-sectional Hubbs-Tait (2009)	112 children 3-5 years old, attending	4.15 (0.55)	2.10 (1.16)	Cognition was evaluated by	Correlation, ANOVA, hierarchical regression	Correlation of blood Pb and cognition scores PPVT-III r^2=-0.004	Concurrent blood Pb in

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
OK, USA *Population may overlap with Hubbs-Tait (2007)*	rural Head Start centers in northern Oklahoma. Year= 2006 Male=52%			Peabody Picture Vocabulary Test–III (PPVT–III) and McCarthy Scales of Children's Abilities (MSCA) test; *Also tested blood Zn and Fe (transferrin receptors)*	child age, parent education, and monthly household income.	MSCA-verbal r^2=0.012 **MSCA-perceptual r^2=-0.241; p<0.01** Hierarchical regression for MSCA-perceptual and blood Pb with home environment-books and library visits (MSCA-verbal and PPVT-III models did not include significant Pb component): **Blood Pb r^2 = 0.36; β=-0.189 (SE=0.75); p<0.05** ANOVA for MSCA-perceptual and blood Pb: <5µg/dL MSCA-P = 45.19 **>5µg/dL MSCA-P = 33.67; p=0.031 to Pb<5** <2.5µg/dL MSCA-P = 46.20 **>2.5µg/dL MSCA-P = 42.29; p=0.048 to Pb<2.5** Authors state MSCA-Verbal and PPVT-III scores were related to iron status and permissive parenting exacerbated negative effects of higher Pb or lower iron	children was significantly associated with lower perceptual cognition scores.
Cross-sectional Hwang (2009) Taiwan	412 steel plant workers in Taiwan (n=17 office workers and n=395 manufacturing workers); Year not stated Male=99.7%	36(6.5)	5.9 (3.4)	Hearing thresholds; *Blood Mn, Cu, Zn, As, Cd also measured*	Logistic regression Age, noise level No effect of gender, cigarette smoking, use of ear protection	<u>Effect of blood Pb on the odds ratio for hearing loss</u> [frequency-OR (95%CI)]: Blood Pb levels ≤4 µg/dL - reference Blood Pb levels 4-7 µg/dL 500-2000 Hz –NA p>0.05 3000 Hz Adj.OR=0.75 (0.17,3.29); p>0.05 4000 Hz Adj.OR=3.54 (1.40, 8.97); p>0.05 6000 Hz Adj.OR=2.11 (0.94, 4.77); p>0.05 8000 Hz Adj.OR=3.0 (0.78, 11.5); p>0.05 Blood Pb levels ≥7 µg/dL 500-2000 Hz –NA p>0.05 **3000 Hz Adj.OR=4.49 (1.28,15.8) p<0.005** **4000 Hz Adj.OR=6.26 (2.35,16.6) p<0.005** **6000 Hz Adj.OR=3.06 (1.27,7.39) p<0.05** **8000 Hz Adj.OR=6.16 (1.59,23.9) p<0.05**	Concurrent blood was significantly associated with hearing loss at sound frequencies of 3000-8000 Hz in steel plant workers.
Prospective Jedrychowski (2008) Krakow, Poland *Population may overlap with Jedrychowski (2009a)*	452 Krakow inner city children born to women attending prenatal clinic in 1st or 2nd trimester; Year=2001-2003 % male not stated	6 months = 26.7(1.6) wks	Cord Pb= 1.42 (0.71)	Cognitive development evaluated using Fagan Test of Infant Intelligence (FTII) assessed visual recognition memory (VRM) by scaled "novelty score": FTII-1=low risk; FTII-2= suspected risk; FTII-3 =high risk	Linear regression; logistic regression; Spearman rank correlation Gestational age, gender of the child, and maternal education	<u>Mean Pb cord blood level by FTII score:</u> Low risk (FTII 1) Pb= 1.38, 95% CI: 1.31-1.45 Suspected risk (FTII 2) Pb= 1.46, 95% CI: 1.26-1.67 High risk (FTII 3) Pb= 1.61, 95% CI: 1.35-1.87 Spearman correlation coefficient for Fagan VRM score and cord blood Pb = **-0.16, p=0.007** <u>FTII higher risk score by cord blood Pb:</u> **Blood Pb (group 3 vs 1and2;continuous by µg/dL):** **Adj. OR (95% CI)= 1.47 (1.07-2.01)** **Blood Pb by 75th percentile (≤1.67 vs >1.67 µg/dL):** **Adj. OR (95% CI)= 2.33 (1.32-4.11)**	Cord blood Pb was significantly associated with lower Fagan visual recognition memory scores and increased scoring in the high-risk group of develop-ment delay in 6-month olds.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Jedrychowski (2009a) Krakow, Poland *Population may overlap with Jedrychowski (2008)*	457 Krakow inner city children born to women attending prenatal clinic in 1st or 2nd trimester; Year=2001-2004 Male =51%	Mother's age: 27.50 (3.52)	Cord: 1.38 (0.59) Girls: 1.41 (0.62) Boys: 1.35 (0.55)	Gender-specific cognitive deficits in first 3 years of life measured by the Bayley Mental Development Index (MDI)	Linear multivariate regression;Generalized Estimating Equations (GEE) longitudinal panel model; Chi-square; analysis of variance Age, gender of child, maternal education, parity, breastfeeding, prenatal and postnatal environmental tobacco smoke	Cord blood Pb level (in quartiles) and MDI scores at 36 months: β (95%CI): Total: 1st: ≤0.99: reference **2nd: 1.00-1.21: -3.494 (-6.214, -0.775); p=0.012** **3rd: 1.22-1.67: -4.459 (-7.223, -1.694); p=0.002** **4th: >1.67: -3.163 (-5.914, -0.412); p=0.024** Boys: 1st: reference **2nd: -5.451 (-9.064, -1.839); p=0.003** **3rd:-8.373 (-12.006, -4.741); p=0.000** **4th: -6.158 (-9.946, -2.370); p=0.002** Girls: 1st: reference 2nd: -1.810 (-5.905, 2.287); p=0.384 3rd: -0.040 (-4.284, 4.203); p=0.985 4th:-0.738 (-4.796, 3.319); p=0.720 Cognitive development of children over follow-up in the GEE models β (95%CI): 1st: reference 2nd: -1.81 (-3.98, 0.35); p=0.100 **3rd: -2.88 (-5.04, -0.71); p=0.009** **4th: -3.00 (-5.22, -0.70); p=0.010** Spearman correlation coefficient at 36 months between cord blood Pb exposure and cognitive function: **Boys: r=-0.239; p=0.0007** Girls: r= -0.058; p=0.432	Cord blood Pb was significantly associated with impaired cognitive function in boys, but not girls.
Prospective Jedrychowski (2009b) Krakow, Poland *Population may overlap with Jedrychowski (2008)*	444 Krakow inner city children born to women attending prenatal clinic in 1st or 2nd trimester; Year= 2001-2004 Male=50.7%	Assessed at 12, 24, 36 months of age	Geometric mean Cord male = 1.30 Cord female =1.28 Cord both = 1.23 Range 0.44-6.9	Mental development assessed using the Bailey Mental Developmental Index (MDI) 2nd edition (BSID-II)	Chi-square, ANOVA, multiple linear regression; generalized estimating equations (GEE) maternal education, parity, gender of child and prenatal ETS exposure	<u>Multiple linear regression for cord blood Pb below <5µg/dL and MDI at various</u> ages: β (95%CI) 12 mo β=-5.42(–11.19, 0.35) p=0.066 **24 mo β=-7.65(–14.68,-0.62)p=0.033** **36 mo β=-6.72(–12.5, -0.89)p=0.024** GEE model of MDI of children from 12-36 months with cord blood Pb <5µg/dL β (95%CI) by log Pb: **β=-6.62 (–1.52, -1.72); p=0.008**	Cord blood Pb was significantly associated with reduced cognitive development (by MDI) at 24 and 36 months.
Prospective Jusko (2008) Rochester, NY, USA *Population may overlap with Canfield (2003b)*	194 children in Rochester, NY; Year = 1994-1995 Male=50%	6	7.2(4.1) avg. 11.4(7.3) peak 5(3.3) 6 yr Exposure assessed at 6, 12, 18 months and 2, 3, 4, 5, and 6 years; Intelligence assessed at 6 years	Intelligence evaluated using Wechsler preschool and primary scale of intelligence-revised (WPPSI-R)	Linear regression Income, sex, mother's education, race, prenatal smoking, birth weight, transferrin saturation, mother's IQ, HOME-SF score	Regression of Blood Pb with WPPSI-R score at age 6: <u>Lifetime average blood Pb</u>: **Full-scale IQ (p-trend =0.006)** **Performance IQ (p-trend =0.002)** Verbal IQ (p-trend =0.11 <u>Concurrent blood Pb (6 years of age):</u> **Full-scale IQ (p-trend =0.03)** **Performance IQ (p-trend =0.004)**	Blood Pb concentrations (concurrent, <24 months, peak, and lifetime average) were significantly

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
and others			of age		Generalized additive model non-linear model for peak blood Pb	Verbal IQ (p-trend =0.28 Infancy blood Pb (6-24 months of age): Full-scale IQ (p-trend =0.05) **Performance IQ (p-trend =0.02)** Verbal IQ (p-trend =0.34) Peak blood Pb: **Full-scale IQ (p-trend =0.03)** **Performance IQ (p-trend =0.02)** Verbal IQ (p-trend =0.19) Children with lifetime average and infancy blood Pb ≥5µg/dL full-scale IQ (4.9 points, p=0.03, 5.2 points, p=0.02 respectively) and performance IQ (4.9 points, p=0.03; 5.4 points, p=0.01 respectively) not verbal IQ (p=0.09, p=0.11 respectively) compared with children with lifetime average blood Pb <5µg/dL. An inverse association (*p* = 0.003) between peak blood Pb levels and full-scale IQ down was supported with nonlinear modeling down to 2.1 µg/dL, the lowest observed peak blood Pb concentration in the study.	associated with decreased full-scale and performance IQ, but not verbal IQ, at age 6.
Case-control Kamel (2002) New England, USA *Population may overlap with Kamel (2003) and others*	109 ALS cases from two major referral centers in Boston, MA and 256 population-based controls (only 41 with Pb measures) identified by random-digit dialing frequency matched by age, sex, and region of residence. Year= 1993-1996 Male= 61%	Range 30-80 Age 30-55 (n=38 cases, 85 controls) Age 56-65 (n=37 cases, 73 controls) Age 66-80 (n=34 cases, 98 controls)	Blood Pb: Median (range) 4.0 (0.5, 14.0) Patella Pb (µg/g): Median (range) 15.0 (0.0, 107) Tibia Pb (µg/g) Median (range) 13.0 (-6.0, 61) Occupational Pb exposure also assessed by self-report (yes/no), and number of days of exposure	Amyotrophic lateral sclerosis (ALS): cases were defined as having received an initial diagnosis by a board-certified neurologist of ALS within the 2 years before enrollment.	Logistic regression Models adjusted for age, square root of age, sex, region, education, and inactivity	Association of self-reported occupational exposure to Pb with ALS: AdjOR (95% CI) Occupational exposure: Not exposed, ref. **Exposed vs: 1.9 (1.1, 3.3)** Lifetime days of Pb exposure: 0 days, ref. 1-399 days: 1.6 (0.6, 3.9) 40-1999 days: 1.9 (0.8, 4.3) **2000+ days: 2.3 (1.1, 4.9)** **Trend: p=0.02** Association of categorical blood and bone Pb with ALS: AdjOR (95% CI) Blood Pb: <1-2 µg/dL, ref. **3-4 µg/dL: 14.3 (3.0-69.3)** **5-14 µg/dL: 24.5 (4.3-139.3)** Patella Pb: -4-9 µg/g, ref. 10-20 µg/g: 2.1 (0.6-7.4) 21-107 µg/g g: 2.8 (0.6-12.4) Tibia Pb: -7-7 µg/g, ref. 8-14 µg/g: 1.6 (0.5-5.6) 15-61 µg/g:1.3 (0.4-4.9) Association of blood and bone Pb as a continuous variable with ALS: AdjOR (95% CI) **Blood Pb: 1.9 (1.4-2.6)** Patella Pb: 3.6 (0.6-20.6) Tibia Pb: 2.3 (0.4-14.5)	Concurrent blood Pb was significantly associated with ALS, while bone Pb associations were not statistically significant. Self-reported occupational exposure to Pb and days of exposure were also significantly associated with ALS.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Case-control Kamel (2003) New England, USA *Population may overlap with Kamel (2002) and others*	103 ALS cases were recruited from two major referral centers in Boston, MA and 38 controls were identified by random-digit dialing frequency matched by age, sex, and region of residence. Year=1993-1996; Male: 61%	mean not reported range 30-80 years	Blood Pb - genotype: *ALAD K59N 1-1*: 3.0 *ALAD K59N 2*: 2.8 *ALAD IVS2 mm*: 2.9 *ALAD IVS2 M*: 2.9 *VDR bb*: 2.9 *VDR B*: 3.0 Patella Pb (µg/g) *ALAD K59N 1-1*: 14.0 *ALAD K59N 2*: 7.3 *ALAD IVS2 mm*: 13.0 *ALAD IVS2 M*: 8.6 *VDR bb*: 12.0 *VDR B*: 12.0 Tibia Pb (µg/g) *ALAD K59N 1-1*: 14.0 *ALAD K59N 2*: 8.6 *ALAD IVS2 mm*: 14.0 *ALAD IVS2 M:* 8.3 *VDR bb:* 13.0 *VDR B:* 13.0	Amyotrophic lateral sclerosis (ALS): cases were defined as having received an initial diagnosis by a board-certified neurologist of ALS within the 2 years before enrollment. Polymorphisms were examined in *ALAD* and *VDR*	Multiple logistic regression Models adjusted for age, square root of age, sex, region, education, and inactivity	Associations of ALS with Pb and genotype: AdjOR (95% CI) **Blood Pb only: 1.9 (1.4-2.6)** **Blood Pb and *ALAD 2*: 2.0 (1.4-2.8)** **Blood Pb and *ALAD I2-2*:1.8 (1.3-2.6)** **Blood Pb and *VDR*: 1.9 (1.4-2.7)** Occupational exposure only: 2.2 (0.68-7.3) Blood and bone Pb only estimates are the same as in (Kamel *et al.* 2002) Patella, Tibia Pb, and occupational exposure to Pb models were not significantly changed with the addition of genotypes to the model None of the genetic polymorphisms were independently associated with ALS alone or in the models with Pb.	The association between concurrent blood Pb was not significantly modified by *ALAD* or *VDR* genotypes, nor were non-significant associations with bone Pb or occupational exposure to Pb.
Case-control Kamel (2005) New England, USA *Population may overlap with Kamel (2002) and others*	103 ALS cases were recruited from two major referral centers in Boston, MA and 38 controls were identified by random-digit dialing frequency matched by age, sex, and region of residence. Year= 1993-1996; % male not stated	mean not reported range 30-80 years	Blood (µg/dL): Case = 5.2 (0.4) Control = 3.4 (0.4) Patella (µg/g): Case = 20.5 (2.1) Control = 16.7 (2.0) Tibia (µg/g): Case = 14.9 (1.6) Control = 11.1 (1.6)	Amyotrophic lateral sclerosis (ALS): cases were defined as having received an initial diagnosis by a board-certified neurologist of ALS within the 2 years before enrollment. Polymorphisms were examined in *ALAD.*	Logistic regression Models adjusted for age, sex, region, education, and inactivity	Complete occupational history of possible Pb exposures generated results virtually identical to the self-reported data in (Kamel *et al.* 2002). Residential and recreational/hobby Pb exposures were not associated with ALS (data not shown). Blood and bone Pb only estimates are the same as in (Kamel *et al.* 2002) *ALAD* polymorphism was not significantly associated with ALS (same results as in (Kamel *et al.* 2003))	Residential and recreational Pb exposures were not associated with ALS. Significant associations of blood Pb and self-reported occupational Pb exposure with ALS were previously reported.
Prospective Kamel (2008) New England, USA *Population may overlap with Kamel (2002) and others*	110 ALS identified through death certificates Year= 1993-1996; Followed for death through 2003 Male= 61%	Median= 60 years Range= 30-79	Median (95% CI): 4.0 (0.5, 14.0)	Amyotrophic lateral sclerosis (ALS) survival: National Death Index Plus and the Social Security Administration Death Index through Dec. 31, 2003.	Cox proportional hazard analysis	Relationship of survival of ALS cases to Pb exposure: AdjHR (95% CI) **Blood Pb** **Diagnosis to death: 0.9 (0.8, 1.0)** **Symptoms to death: 0.9 (0.8, 1.0)** Patella Pb **Diagnosis to death: 0.5 (0.2, 1.0))** Symptoms to death: 0.6 (0.3, 1.2) Tibia Pb	Shorter survival from diagnosis to death had an inverse non-statistically significant association with blood Pb, patella Pb, tibia

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Diagnosis to death: 0.3 (0.1, 0.7) Symptoms to death: 0.3 (0.2, 0.7) Occupational Pb exposure Diagnosis to death: No (referent) Yes: 0.7 (0.5, 1.2) Symptoms to death: No (referent) No: referent Yes: 0.7 (0.4, 1.2)	Pb, and occupational Pb exposure.
Cross-sectional Kim(2009) Korea *Population may overlap with Kim (2010)*	261 children from four areas in Korea (Seoul, Ulsan, Seongnam, and Yeoncheon); Year=2007; % male not stated	9.7 (0.6)	1.73(0.8)	Cognitive function assessed using the abbreviated Korean Educational Development Institute-Wechsler Intelligence Scales (KEDI-WISC), blood Mn	Chi-square, student's t-test, ANOVA, linear and multiple linear regression The age, sex, maternal and paternal education, yearly family income, maternal smoking during pregnancy, birth weight, mother's age at birth, and indirect smoking	Linear regression analysis of blood Pb and IQ: **Full-scale IQ β =-0.174, p = 0.005** **Verbal IQ β = -0.187, p = 0.003** Performance IQ β = --0.104; p = 0.106 Additive interaction of blood Pb and Mn on IQ: Full-scale IQ **Blood Pb β =-0.17; p <0.001** **Blood Mn β =-0.12; p < 0.05** Verbal IQ **Blood Pb β =-0.19; p <0.001** **Blood Mn β =-0.12; p < 0.05** Performance IQ β = --0.104; p = 0.106 Blood Pb β =-0.10; p >0.05 Blood Mn β =-0.08; p > 0.05 Blood Mn was also associated with reduced Full-scale, and verbal IQ measures. Negative effect of Pb on IQ was not observed in children with blood Mn<1.4µg/dL; authors suggest additive interaction and effect modification by blood Pb and Mn.	Concurrent blood Pb was significantly associated with reduced cognitive function at age 9.
Cross-sectional Kim (2010) Korea *Population may overlap with Kim (2009)*	275 third and fourth grade children from one school in each town: Seoul, Seongnam, Ulsan, and Yeoncheon; Year = 2007 Male = 53.1%	9.7 (0.6) years Range: 8-10	All (Geom. mean): 1.5 (SD 1.6) µg/dL Median: 1.6 Range:0.4-4.9 4^{th} quartile > 2.18 Girls (Geom. mean): 1.4 (SD 1.53) µg/dL Range:0.44-3.19 Boys (Geom. mean): 1.7 (SD 1.58) µg/dL Range:0.42-4.91	Inattention-hyperactivity and Neurocognitive profiles: Teachers completed the Attention-Deficit Hyperactivity Disorder Rating Scale IV, Parents completed the Korean version of the Learning Disability Evaluation Scale, and children performed neurocognitive tests: the Continuous Performance Test (CPT), the Children's	Linear regression analysis for log blood Pb Logistic regression analysis for high (>2.18µg/dL) and low (<2.18) Pb levels and *t*-test of difference Adjusted for sex, SES, parental education, secondhand smoke, and smoking during pregnancy	Regression within blood Pb catagories high Pb (≥2.18); low Pb (<2.18): $_{adj}B$ (95% CI) ADHD rating scale Inattention: 1.8 (-1.3, 4.9); **-2.45 (-4.3, -0.6) *p* < 0.01** Hyperactivity: 0.7 (-2.1, 3.5); -1.10 (-2.6, 0.4) Total score: 2.5 (-3.0, 8.0);**-3.54 (-6.7, -0.4) *p* < 0.05** Learning Disability Evaluation Test Listening: -1.0 (-2.4, 0.3); 0.56 (-0.1, 1.3) Thinking: -0.8 (-1.9, 0.4);**0.62 (-0.01, 1.2) *p* < 0.05** Talking: -1.0 (-2.4, 0.3); **0.89 (0.2, 1.6) *p* < 0.01** **Reading: -1.6 (-3.0, -0.2) *p*<0.05; 0.9 (0.1, 1.7) *p*<0.05** Writing: -1.2 (-2.6, 0.2); **0.98 (0.2, 1.7) *p* < 0.01** Spelling: -1.4 (-2.9, 0.1); **0.89 (0.1, 1.7) *p* < 0.05** **Calcul.: -1.6 (-2.9, -0.2) *p*<0.05; 0.82 (0.1, 1.6) *p*<0.05** Visual Continuous Performance Test **Omission errors: 15.5 (1.1, 29.8) *p* < 0.05; -8.38 (-16.2, -0.6) *p* < 0.05** Commiss. errors: -3.5 (-20.2, 13.3); -2.99 (-10.6, 4.6)	Concurrent blood Pb was significantly associated with inattentive and hyperactivity symptoms and learning difficulties in 8-10 year old children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				Color Trails Test, and the Stroop Color and Word Test.		Reaction time: 4.0 (-4.8, 12.8); -1.11 (-4.9, 2.6) React time var.: 1.6 (-19.8, 23.0); -5.08 (-14.7, 4.5) Children's Color Trail Test CCTT-1 total time: 4.4 (-7.6, 16.4); not reported CCTT-2 total time: -1.1 (-7.8, 5.6); not reported Difference interference: 0.2 (-5.9, 6.4); 1.78 (-1.4, 4.9) Stroop Word and Color Test Word reading: -2.9 (-8.8, 3.0); not reported Color naming: -5.2 (-11.8, 1.4); not reported Color–word: -7.2 (-14.2, -0.3) $p < 0.05$; not reported Interference: -1.2 (-9.0, 6.5); -1.03 (-4.4, 2.2)	
Cross-sectional Kordas (2004) Torreón, Mexico *Population may overlap with Kordas (2006) and others*	724 children attending first grade at one of 9 public school and living near a metal foundry in Mexico; Year=2001 Male=54%	Range = 6.2 to 8.5 years	11.5 (6.1) µg/dL	Cognitive outcomes were measured using 14 tasks designed to assess specific and global aspects of cognition: Cognitive Abilities Test (CAT), the Wechsler Intelligence Scale for Children-Revised Mexican Version (WISC-RM) Coding, Digit Retention and Arithmetic; Number and Letter Sequencing, a computer-based Test of Cognitive Abilities, Math Achievement Test, a Test of Visual-Spatial Abilities and the Peabody Picture Vocabulary Test (PPVT)	Multiple regression models; regression coefficients Gender, age, socioeconomic status, school, Hb, ZPP, and Ferritin	Multiple regression models of concurrent blood Pb and PPVT performance in the first-grade: **β=-0.371; p=0.005**	Blood Pb was significantly associated with the lower PPVT scores in children 6-8 years old.
Cross-sectional Kordas (2006) Torreón, Mexico *Population may overlap with Kordas (2004) and*	532 children attending first grade at one of 9 public school and living near a metal foundry in Mexico; Year= 2001	Range = 6.2 to 8.5 years	All: 11.4 (6.1) Girls: 11.1 (5.8) Boys: 11.7 (6.4)	Cognitive function on 14 tasks that assess specific and global aspects of cognition: Math achievement test, Peabody picture vocabulary test,	Spline (segmented), and logistic regression models in stratums of Pb exposure. Child's age, gender, hemoglobin, family	<u>Adjusted change in cognitive performance for every 1 µg/dL increase in blood Pb (below the cutpoint):</u> Linear regressions: β (95% CI) Math (10µg/dL): -0.42 (-9.2, 0.08) PPVT (12µg/dL): -0.71 (-1.43, 0.02), p<0.01 Distractibility (freedom) (12µg/dL): -0.40 (-1.17, 0.37) Sequencing (10µg/dL): -0.20 (-0.50, 0.10)	Concurrent blood Pb level (below 12µg/dL) was associated with poorer cognitive

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
others	Male=54%			freedom from distractibility factor, sequencing, Sternberg memory, figure matching and design, visual search, cognitive abilities test (CAT): stimulus discrimination, and visual memory span	possessions, forgetting homework, house ownership, crowding, maternal education, birth order, family structure, arsenic exposure, tester, and school	Sternberg (10µg/dL): -0.16 (-0.37, 0.05) Figure matching (10µg/dL): -0.20 (-0.47, 0.06) **Figure Design (12µg/dL): -0.31 (-0.62, -0.01), p<0.05** Visual search correct (10µg/dL): -0.01 (-0.52, 0.51) CAT mean decision time (10µg/dL): 0.05 (-0.07, 0.17) Logistic regressions: OR (95% CI) Visual search err. (10µg/dL): 1.09 (0.92, 1.28), p<0.1 Stimulus discrim. correct (8µg/dL): 0.85 (0.63, 1.13) Visual mem. span correct (10µg/dL): 0.90 (0.74, 1.10) CAT number of errors (14µg/dL): 1.06 (0.96, 1.17)	performance on a figure design task to assess cognition. Regression slopes were steeper at lower blood Pb levels.
Cross-sectional Kordas (2007) Torreón, Mexico *Population may overlap with Kordas (2004) and others*	550 children attending first grade at one of 9 public school and living near a metal foundry in Mexico; Year=2001 Male= 54%	6.9 (0.4) years	11.5 (6.1)	Micronutrient status, sleep, classroom behavior, and activity	Regression analysis Behavior outcome: age, sex, economic, status, home ownership, crowding, maternal education, family structure, and parent's involvement in schooling Sleep: heightened anxiety, bedroom sharing, and who decided on child's sleep and wake-up time, age, sex, and crowding in the home	AdjOR (95% CI)/ β(95% CI) between blood Pb, physical activity and sleep (blood Pb <10µg/dL vs ≥10µg/dL) <u>Sleep characteristic</u> Bedtime (min): β (95% CI)=-5.0 (-12.0, 1.9) **Wake up time: β (95% CI)=9.6 (5.7, 13.5); p<0.01** Sleep latency: OR (95% CI)= 1.2 (0.8, 1.8) **Daily sleep: OR (95% CI)= 2.6 (1.0, 6.5); p<0.05** Wakes at night: OR (95% CI)=1.0 (0.7, 1.5) Poor sleeper: OR (95% CI)=0.9 (0.6, 1.4) Low morning energy: OR (95% CI)=1.2 (0.8, 1.7) Wants to sleep more: OR (95% CI)= 1.3 (0.9, 1.9) Fussy: OR (95% CI)=1.4 (0.9, 2.2) Tired before 4PM: OR (95% CI)=0.7 (0.4, 1.2) Nap >3 d/wk: OR (95% CI)=0.8 (0.5, 1.4) Nap ≥ 1h/d: OR (95% CI)=1.0 (0.7, 1.4) <u>Observed Behavior</u> On task: β (95% CI)=0.6 (-3.2, 4.5) Off-task active: β (95% CI)= -1.9 (-4.9, 1.0) Off-task passive: β (95% CI)= 1.3 (-1.2, 3.8) <u>Activity at recess:</u> β (95% CI)=-3.6 (-8.6, 1.3)	Blood Pb was significantly associated with later waking time and shorter duration of sleep.
Cross-sectional Krieg (2009) USA *Population may overlap with Lanphear (2000) and others*	2,611 to 2,823 people by endpoint from NHANES III; Year = 1991-1994 % male not stated	20-59 years	2.88(SE 0.13) Measured when outcome assessed	Neurobehavioral test performance (simple reaction time, symbol-digit substitution, and serial digit learning), serum folate, homocysteine, vitamin B12	Linear Regression Age, sex, education, family income, race-ethnicity, computer or video game familiarity, alcohol use within the last 3 h, and test language	Regression of log blood Pb and test performance: slope (SE), p-value simple reaction time (mean ms)= -0.38(6.23); p=0.95 symbol-digit substitution mean total latency (s) =0.11(0.46); p=0.82 number of errors =-0.33(0.23); p=0.16 serial digit learning performance trials to criterion =-0.22(0.25);p=0.39 total score = -0.52(0.48);p=0.29 Log serum homocysteine and log blood Pb (p=0.0015) Authors state simple reaction time, symbol-digit substitution and serial digit learning performance was not related to serum folate or serum vitamin B12.	Blood Pb level was not significantly associated with neuro-behavioral test performance in adults.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Cross-sectional Krieg (2005) USA *Population may overlap with Krieg (2009) and others*	4,937 adults aged 20-59 years from NHANES III. Year=1991-1994; Male = 46%	20-59 years	NHANES III: Geom. mean 2.51 Arith. mean 3.30 Range: 0.7-41.8	Neurobehavioral tests: Simple reaction time, Symbol-digit substitution, and Serial digit learning Also performed meta-analysis of 26 occupational studies (all with exposed blood Pb >15µg/dL)	Regression analysis Sex, age, education, family income, race-ethnicity, computer or video game familiarity, alcohol use, test language, and survey phase	Relationship between test performance and log10 blood Pb from NHANES III: Adjusted Slope (SE); *p* Simple reaction time Mean reaction time(ms): 4.65 (3.95); *p*=0.2440 Symbol-digit substitution: Mean total latency(s): 0.40 (0.36); *p*=0.2745 Number of errors: -0.04 (0.16); *p*=0.8172 Serial digit learning Trials to criterion: -0.18(0.16); *p*=0.2567 Total score: -0.45 (0.38); *p*=0.2361	Concurrent blood Pb was not significantly associated with performance on the three neurobehavioral tests
Cross-sectional Krieg (2009) USA *Population may overlap with Lanphear (2000) and others*	Subjects were selected from NHANES III. There were 842 Children (age 12-16 years), 2093 adults (age 20-59 years), and 1799 older adults age ≥60 years Year=1991-1994 % male not stated	12-16, 20-59, and 60+	Mean (SE) blood Pb concentration by age group: 12-16 years: 1.95 (0.16) 20-59 years: 2.85 (0.16) 60 + years: 4.02 (0.06)	Cognitive function was measured by the Wechsler Intelligence Scale for Children-Revised (WISC-R) and the Wide Range Achievement Test-Revised (WRAT-R); genotypes *ALAD* rs1800435: CC/CG vs GG for each age-group. Serum homocysteine also measured in adults.	Regression analyses Children: sex, education of family reference person, family income, race-ethnicity, and test language Adults: sex, age, education, family income, race-ethnicity, computer or video game familiarity, alcohol use in the last 3 hours, and test language Older adults: sex, age, education, family income, race-ethnicity, and test language	Adjusted mean Blood Pb was higher in GG than CC/CG, with only in **children age 12-16 reaching statistical significance: 2.02, 1.28 (p=0.0175)** Regression analysis between measures of cognitive function and log blood Pb: Slope (SE), *p* 12-16 year olds: WISC-R Block design scaled score: **All: -1.50 (0.58); *p*=0.0165** *ALAD* CC/CG: -2.65 (1.64); *p*=0.1206 ***ALAD* GG: -1.31 (0.63); *p*=0.049** Interaction: F = 0.54, *p* = 0.4707 WISC-R Digit span scaled score: **All: -1.86 (0.53); p=0.0018** *ALAD* CC/CG: -3.14 (2.29); *p*=0.1835 ***ALAD* GG: -1.67 (0.49); *p*=0.0022** Interaction: F = 0.44; *p* = 0.5136 WRAT-R Reading standardized score: **All: -12.77 (2.18); p=0.0005** *ALAD* CC/CG: -19.29 (11.95); *p*=0.1201 ***ALAD* GG: -11.80 (3.06); *p*=0.0008** Interaction: F = 0.41; *p* = 0.5275 WRAT-R Math standardized score: **All: -11.08 (4.55); p=0.0231** *ALAD* CC/CG: -16.37 (17.88); *p*=0.3695 ***ALAD* GG: -9.86 (4.76); *p*=0.0498** Interaction: F = 0.13; *p* = 0.7169 Ages 20-59 years: Simple reaction time, Mean reaction time: All: -6.33(7.10); p=0.3820 ***ALAD* CC/CG: -38.24 (17.87); *p*=0.0432** *ALAD* GG: -2.06 (7.61); *p*=0.7892 **Interaction: F = 4.28; *p* = 0.0499** Symbol-digit substitution, Mean total latency(s) :	Previously reported significant associations of concurrent blood Pb with decreases in WISC-R and WRAT-R cognitive measures in children 12-16 were not modified by *ALAD* genotype. No significant differences were found between blood Pb and cognitive function in adults - except in 20 - 59 year olds' mean reaction time decreased as blood Pb increased in the *ALAD* rs1800435 CC/CG group (an improvement in

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						All: 0.93 (0.55); *p*=0.1054 *ALAD* CC/CG: 2.71 (1.46); *p*=0.0756 *ALAD* GG: 0.68 (0.56); *p*=0.2377 Interaction: F = 1.89; *p* = 0.1825 Symbol-digit substitution, Number of errors: All: 0.00 (0.19); *p*=0.9815 *ALAD* CC/CG: 0.58 (0.32); *p*=0.0822 *ALAD* GG: -0.19 (0.22); *p*=0.3862 Interaction: F = 3.59; *p* = 0.0707 Serial digit learning, Trials to criterion: All: -0.02(0.29); *p*=0.9556 *ALAD* CC/CG: -0.77 (0.72); *p*=0.2927 *ALAD* GG: 0.06 (0.28); *p*=0.8339 Interaction: F = 1.29; *p* = 0.2679 Serial digit learning, Total score: All: -0.03(0.67); *p*=0.9622 *ALAD* CC/CG: -1.11 (1.38); *p*=0.4302 *ALAD* GG: 0.05 (0.66); *p*=0.9406 Interaction: F = 0.78; *p* = 0.3863 60+ years: Word recall (number correct) : All: -0.06(0.06); *p*=0.2941 *ALAD* CC/CG: 0.02 (0.17); *p*=0.9063 *ALAD* GG: -0.06 (0.08); *p*=0.4403 Interaction: F = 0.15; *p* = 0.6991 Story recall (number correct) : All: -0.05(0.15); *p*=0.7345 *ALAD* CC/CG: -0.88 (0.55); *p*=0.1242 *ALAD* GG: 0.16 (0.17); *p*=0.3531 Interaction: F = 3.15; *p* = 0.0890	performance).
Cross-sectional Krieg (2010) USA *Population may overlap with Lanphear (2000) and others*	Children aged 12 to 16 (n=842), adults aged 20-59 (n=2093), and adults over 60 years old (n=1799) from NHANES III; Year= 1991-1994 % male not stated	Subjects selected from age ranges and no mean age is reported within these groups	<u>Age 12-16:</u> 1.95 (SE 0.16) Range 0.7-39.8 <u>Age 20-59:</u> 2.85 (SE0.16) Range 0.7-28.1 <u>Over 60:</u> 4.02 (SE 0.08) Range 0.7-52.9 Blood Pb did not change by *VDR* genotype	Cognitive tests including components of WISC-R and WRAT-R (children), neurobehavioral test components from NES2 (adults 20-59), and word and story recall (adults over 60) *Also studied interaction of test-Pb association with VDR*	Log linear regression model All adjusted for sex, education (of caregiver in children), family income, race-ethnicity, and test language Adults aged 20-59 also adjusted for age, computer/video game familiarity, and alcohol use in last 3 hours	<u>Age 12-16 slope (95%CI) for test and log Blood Pb:</u> **Block design (WISC-R): -1.50 (-2.69, -0.30), p=0.0165** **Digit span (WISC-R): -1.86 (-2.96, -0.77), p=0.0018*** **Reading (WRAT-R): -12.77 (-19.35, -6.20), p=0.0005** **Math (WRAT-R): -11.08 (-20.49, -1.67), p=0.0231*** <u>Age 20-59 slope (95%CI) for test and log Blood Pb:</u> Reaction time: -6.33 (-21.03, 8.63), p=0.3820 Symbol-digit latency: 0.93 (-0.21, 2.07), p=0.1054 Symbol-digit errors: 0.00 (-0.38, 0.39), p=0.9815* Serial digit trials: -0.02 (-0.62, 0.59), p=0.9556 Serial digit total: -0.03 (-1.41, 1.35), p=0.9622 <u>Over 60 slope (95%CI) for test and log Blood Pb:</u> Word recall: -0.06 (-0.19, 0.06), p=0.2941 Story recall: 0.05 (-0.26, 0.37), p=0.7345	Some *VDR* genotypes modified the relationship between blood Pb and several cognitive tests including WISC-R digit span, others did not significantly alter previously reported associations of blood Pb with

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				genotypes and blood Pb association with serum homocysteine	Adults over age 60 also adjusted for age	*Results showed significant interaction with VDR genotype *[Cognitive function and Pb findings are consistent with previous reports in these subjects by Lanphear (2000) and Kreig (2009)]*	impaired cognitive function in children but not adults.
Cross-sectional Lanphear (2000) USA *Population may overlap with Krieg (2009) and others*	4,853 children from NHANES III Year=1988-1993 % male not stated	Range: 6 – 16 years	Geometric mean: 1.9 µg/dL Exposure measured when outcome assessed	Intelligence measured by the Arithmetic and Reading subtests of the Wide Range Achievement Test (WRAT-R) and the Block Design and Digit Span subtests of the Wechsler Intelligence Scale for Children (WISC-R).	Multivariate analysis; multiple linear regression analyses. Gender, race/ethnicity, poverty, region of the country, parent or caregiver's marital status, serum ferritin level, serum cotinine level, *in utero* and post natal exposure to tobacco, birthweight, admission to a NICU.	<u>Adjusted regression of cognitive/academic test scores and blood Pb < 10µg/dL</u>: Arithmetic **coefficient (SE) = -0.70 (0.17); p< 0.001** Reading **coefficient (SE) = -0.99 (0.19); p< 0.001** Block Design **coefficient (SE) = -0.10 (0.04); p= 0.009** Digit Span **coefficient (SE) = -0.05 (0.02); p= 0.04** <u>Adjusted regression of cognitive/academic test scores and blood Pb <5µg/dL</u>: Arithmetic **coefficient (SE) = -1.06 (0.48); p= 0.03** Reading **coefficient (SE) = -1.66 (0.36); p< 0.001** Block Design coefficient (SE) = -0.05 (0.07); p= 0.45 Digit Span coefficient (SE) = -0.09 (0.07); p= 0.20	Blood Pb below 10µg/dL was significantly associated with deficits in cognition and academic skills in children, while those below 5µg/dL were only significantly associated with deficits in arithmetic and reading.
Pooled analysis Lanphear (2005)	Pooled analysis of 7 prospective studies of blood Pb and IQ in children initiated before 1995 (n=1,333): Boston (Bellinger (1992)), Cincinnati (Dietrich (1993b)), Cleveland (Ernhart (1989)), Mexico City (Schnaas, (2000)), Port Pirie Australia (Baghurst (1992)), Rochester (Canfield (2003a)), and Yugoslavia (Wasserman (1997)).	Birth through 10 years of age. [ages for individual studies not stated]	<u>Median (5^{th} – 95^{th}):</u> Concurrent 9.7 (2.5 – 33.2) Peak 18.0 (6.2 – 47.0) Early childhood 12.7 (4.0 – 34.5) Lifetime average 12.4 (4.1 – 34.8)	IQ score as measured by Wechsler Intelligence Scales for Children, Wechsler Preschool and Primary Scales of Intelligence.	Multiple regression analysis; univariate regression analysis Child's sex, birth order, birth\ weight, maternal education, maternal age, marital status, prenatal alcohol exposure, HOME Inventory score.	<u>Mean adjusted changes in full-scale IQ score associated with an increase in blood Pb concentration (log scale), from the 5^{th} to 95^{th} percentile* of the concurrent blood Pb level at the time of IQ testing</u>: **Early childhood β(95% CI)=-2.04 (-3.27, -0.81)** **Peak β(95% CI)=-2.85 (-4.10, -1.60)** **Lifetime average β(95% CI)=-3.04 (-4.33, -1.75)** **Concurrent β(95% CI)=-2.70 (-3.74, -1.66)** *5^{th} and 95^{th} percentiles listed with these results differed from those in another table included in the Blood Pb column.	Early childhood, peak, lifetime average and concurrent blood Pb was significantly associated lower IQ score in a pooled analysis of 7 prospective cohort studies.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Leviton (1993) Boston, MA, USA *Population may overlap with Bellinger (1994b)*	1923 children born at the Lying-In Division of the Boston Hospital for Women; Year= 1979-1980 Male=50%	8 years	Cord blood Pb 6.8 µg/dL Tooth (dentin) Pb 2.8 µg/g	Boston Teachers Questionnaire (BTQ) to assess academic performance and behavior.	Multivariate analysis Single-parent family, gestational age <37 weeks, mother not a college graduate, self-identification as black, only one child in family, and day care during first 3 years	Risk Ratios (95% CI) for cognitive performance at age 8 with cord blood Pb levels (≥10µg/dL vs <10µg/dL): Girls **Tasks : 2.1 (1.0, 4.4)** **(dependent, impersistent, inflexible and inappropriate approach)** Behavior, hyperactivity, reading, arithmetic, directions, and daydreaming not significant Boys **Arithmetic: 1.6 (1.0, 2.8)** **Directions: 2.7 (1.4, 5.2)** **Tasks: 2.3 (1.2, 4.5)** Behavior, hyperactivity, reading, and daydreaming NS Risk Ratios (95% CI) for cognitive performance at age 8 with dentin Pb content (≥5µg/g vs <5µg/g) Girls **Reading: 2.1 (1.1, 4.2)** **Daydreaming: 2.0 (1.1, 3.5)** **Tasks: 2.3 (1.1, 5.0)** Behavior, hyperactivity, arithmetic, and directions NS Boys: None were statistically significant	Cord blood Pb over 10µg/dL was statistically significantly associated with task difficulty in girls, and arithmetic, directions, and task difficulty in boys. Dentin Pb was statistically significantly associated with reading, task difficulties and daydreaming in girls, but not in boys.
Case-control (Louis *et al.* 2003) New York, NY, USA *Population may overlap with (Louis et al. 2005) and (Louis et al. 2011)*	100 Essential tremor (ET) patients from the Neurological Institute of New York, Columbia-Presbyterian Medical Center (CPMC) and 143 controls from random-digit dialing frequency matched on age, sex, and ethnicity. Year= 2000-2004 (from (Louis *et al.* 2011)); Male: Cases: 46% Controls: 21%	68 years Cases: 70.7 (9.9) yrs Controls: 66.2 (9.7) yrs	2.89 Cases: 3.3 (2.4) Controls: 2.6 (1.6)	Essential Tremor (ET) diagnosis examination of cases and controls by the treating neurologist at the Neurological Institute of New York, Columbia-Presbyterian Medical Center	Mann-Whitney non-parametric test Spearman's correlation with total tremor score Logistic regression Age, sex, ethnicity, years of education, number of rooms in home, number of cigarette pack-years, and current reported consumption of vitamin C, calcium, and iron	Blood Pb in cases and controls: median **Cases=2.7, Controls=2.3; z = 2.08, p = 0.038** Correlation between total tremor score and blood Pb: **All subjects: r = 0.14, p = 0.03** ET cases: r = 0.07, p = 0.48 Association of unit increase in blood Pb and ET diagnosis: AdjOR (95%CI) Control: reference **Cases: 1.19 (1.03, 1.37); p=0.02**	Concurrent blood Pb was significantly associated with essential tremor.
Case-control (Louis *et al.* 2005) New York, NY,	63 Essential tremor (ET) patients from the Neurological	Cases: 67.4 (16.6) yrs Controls	2.88 Cases: 3.5 (2.2)	ET diagnosis from the treating neurologist at the Neurological	X^2 and Fisher's exact test Logistic regression, Pearson's correlation	Blood Pb in cases and controls: mean **Cases=3.5, Controls=2.6; p = 0.007**	Concurrent blood Pb was significantly

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
USA *Population may overlap with (Louis et al. 2003) and (Louis et al. 2011)*	Institute of New York, Columbia-Presbyterian Medical Center (CPMC) and 101 controls from random-digit dialing frequency matched on age, sex, and ethnicity. Year= 2000-2004 (from (Louis *et al.* 2011)); Male: Cases: 57.1% Controls: 43.6%	64.9 (11.1) yrs	Controls: 2.5 (1.5) Mean log blood Pb concentration by *ALAD* allele and diagnosis: *ALAD* 1/1 (N=129) Cases: 2.63 (1.82) Controls: 2.29 (1.78) *ALAD* 1/2 or 2/2 (N=35) Cases: 3.8 (1.78) Controls: 2.0 (1.78)	Institute of New York, Columbia-Presbyterian Medical Center	Analysis adjustments included age, family history of ET, and sex	*ALAD* genotype and ET: n (%); OR (case vs. control) 1/1: 45 cases (71.4%), 84 controls (83.2%) 1/2 or 2/2: 18 cases (28.6%), 17 controls (16.8%) OR = 1.98 (95% CI 0.93-4.21), *P* = 0.077 Logistic model of ET including *ALAD* 2 allele, log blood Pb concentration, and an *ALAD*xblood Pb interaction: **Interaction: AdjOR = 7.81 (1.08-4789.68), *P* = 0.046** Stratified by genotypes: OR (95% CI), *P* *ALAD* 1/1: 2.69 (0.61-11.82), *P* = 0.19 ***ALAD* 1/2 or 2/2: 80.29 (3.08-2,096.36), *P* = 0.008** Proportion of subjects with *ALAD* 2 allele by blood Pb tertile: n/total (%) cases; controls Lowest (≤2µg/dL): 2/14 (14.3%); 9/41 (22.5%) Middle (2.04-3.236µg/dL): 2/22 (9.1%); 3/32 (9.4%) Highest (≥3.3µg/dL): 14/27 (51.9%); 5/28 (17.9%)* ***Fisher's exact test, *P* = 0.009** Logistic model of ET including *ALAD* 2 allele, log blood Pb tertile, and an *ALAD*xblood Pb tertile interaction: **Interaction: OR = 2.92 (95% CI 1.05-8.12), *P* = 0.04** Stratified by genotypes: OR (95% CI), *P* *ALAD* 1/1: 1.23 (0.78-1.96), *P* = 0.37 ***ALAD* 1/2 or 2/2: 3.60 (1.45-8.97), *P* = 0.006** Correlation of log blood Pb with total tremor score: Pearson's *r*, *P*-value **Cases 0.27, *P*=0.03**; Controls -0.01, *P*=0.91 **Adjusted for age and ET meds, Case 0.28, *P*=0.03** 1/1: Cases 0.20, *P*=0.20; Controls not reported 1/2 or 2/2: Cases 0.43, *P*=0.07; Controls 0.03, *P*=0.76 **Adjusted for age and ET meds, Case 0.66, *P*=0.005**	associated with essential tremor, particularly in subjects carrying the *ALAD* 2 allele.
Case-control (Louis *et al.* 2011) New York, NY, USA *Population may overlap with (Louis et al. 2003) and (Louis et al. 2005)*	106 Essential tremor (ET) patients from the Neurological Institute of New York, Columbia-Presbyterian Medical Center (CPMC) and 151 controls from random-digit dialing frequency	All: 65.8 (13.8) yrs Cases: 68.2 (15.2) yrs Controls: 64.1 (12.5) yrs	Blood Pb All: 2.9 (1.8) Cases: 3.1 (2.1) Controls: 2.7 (1.6) Blood harmane: mean (SD) (g^{-10}/ml) All: 0.17 (0.74) Cases: 0.20 (0.77) Controls: 0.15 (0.72) Blood Pb and	Total tremor score: clinical measure of tremor severity; ranges from 0-36. ET diagnosis from the treating neurologist at the Neurological Institute of New York, Columbia-Presbyterian Medical Center. Blood harmane (1-methyl-	Spearman's correlations and Kruskal-Wallis non-parametric tests; Multivariate linear regression; Age, gender, white race and cigarette pack-years	Spearman's Correlations: **Blood Pb and total tremor score: p=0.045** **Blood harmane and total tremor score: p=0.007** Total tremor score by toxicant group: mean (SD) Group 1: ↓harmane and ↓ Pb: 8.4 (8.2) Group 2: ↑harmane and ↓ Pb: 10.8 (10.0) Group 3: ↓ harmane and ↑ Pb: 10.1 (9.6) Group 4: ↑ harmane and ↑ Pb: 13.7 (10.4) **Kruskal-Wallis, p-0.028** Group 1: ↓harmane and ↓ Pb: 8.4 (8.2) Group2 + Group 3: 10.5 (9.8) Group 4: ↑ harmane and ↑ Pb: 13.7 (10.4)	Blood Pb and blood harmane were significantly associated with total tremor score in combination – suggesting an additive effect.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	matched on age, sex, and ethnicity. Year= 2000-2004 Male:43.2%		harmane were not correlated (r = 0.008, p = 0.90)	9H-pyrido[3,4-β]indole) was also measured.		**Kruskal-Wallis, p=0.01** Linear regression for log-tremor score and toxicant group: β, p **Unadjusted: β=0.116, p = 0.006** **Adj. age: β=0.098, p = 0.02** **Fully adjusted: β=0.087, p = 0.04** Restricted to ET cases (n=106) Total tremor score by toxicant group: mean (SD) Group 1: ↓harmane and ↓ Pb: 17.3 (5.5) Group2 + Group 3: 20.1 (8.1) Group 4: ↑ harmane and ↑ Pb: 22.3 (7.1) Kruskal-Wallis, p=0.08 Restricted to ET cases (n=106) Linear regression for log-tremor score and toxicant group: β, p **Unadjusted: β=0.06, p = 0.01** **Fully adjusted: β=0.06, p = 0.018** Restricted to controls (n=151) Total tremor score by toxicant group: mean (SD) Group 1: ↓harmane and ↓ Pb: 3.5 (2.3) Group2 + Group 3: 3.9 (2.9) Group 4: ↑ harmane and ↑ Pb: 4.8 (3.1) Kruskal-Wallis, p=0.24 Restricted to controls (n=151) Linear regression for log-tremor score and toxicant group: β, p Unadjusted: β=0.06, p = 0.16 Fully adjusted: β=0.05, p = 0.26	
Meta-analysis Marcus (2010)	Meta-analysis of 18 studies of Pb and conduct problems in children and adolescents (n=8561): 11 blood Pb (Braun (2008), Burns (1999), Chen (2007), Chiodo (2004) and (2007), Dietrich (2001), Nigg (2008), Sciarillo (1992), Thomson (1989), Wasserman (2001),and Yule (1984)), 2 tooth Pb (Bellinger (1994b) and Needleman	Blood Pb: Braun08: 12.0 Burns99: 12.0 Chen07: 7.0 Chiodo04: 7.8 Chiodo07: 6.9 Dietrich01: 15.6 Nigg08: 13.3 Sciarillo92: 3.8 Thoms.89: 9.5 Wasser.01: 4.5 Yule84: 8.5 Tooth Pb: Bellinger94: 7.0 Needle.90: 18.4 Hair Pb: Marlowe82: 9.7	Blood Pb: Burns , 1999: Females = 14.3 Males = 13.9 Chen, 2007: 26.0 Chiodo, 2004: 5.4 Chiodo, 2007: 5.0 Dietrich, 2001: 1.2 Nigg:, 2008: 1.0 Sciarillo, 1992: 18.0 Thomson, 1989: 10.4 Wasserman, '01: 9.6 Yule, 1984: 13.5	Conduct Problem measures varied by study, including BASC-PRS, BASC-TRS, CBCL, CBCL-Ex, CR, CRS, CRS-CP, MHDS-CD, NYS, PRDB, RS, SDB, SRA, TRF-DB, TRF-Ex, WPIC-Ag, WPIC-P, and WPIC-T.	Pearson's product-moment correlation coefficients corrected for bias using a Fisher's Zr transformation converted back to r Effect sizes weighted by samples size with the inverse variance weight (sample size - 3) Maximum likelihood random effects model and a Q test of homogeneity Adjustments varied by study and included sex,	Correlation coefficient of Pb and conduct problems (Adjusted effect): r Blood Pb: Braun, 2008: 0.07 Burns , 1999: Females 0.35 Males 0.27 Chen, 2007: 0.18 Chiodo, 2004: 0.14 (0.12) Chiodo, 2007: 0.10 (0.09) Dietrich, 2001: 0.10 Nigg:, 2008: 0.18 Sciarillo, 1992: 0.17 Thomson, 1989: 0.07 Wasserman, 2001: (0.32) Yule, 1984: 0.16 Tooth Pb: Bellinger, 1994: 0.12 (0.09)	Blood, bone, and tooth Pb were significantly associated with increased in conduct problems in a meta-analysis of 15 studies. Three studies that measured hair Pb had larger effect sizes and were not included in the final meta-analysis.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	(1990)), 3 hair Pb (Marlowe (1982), (1985), and (1993)), and 2 bone Pb (Needleman (2002) and (1996))	Marlowe85: 8.4 Marlowe93: 3.5 Bone Pb: Needle.96: 12.0 Needle.02: 15.7			race/ ethnicity, maternal marital status, sibship size, birth order socioeconomic status, social class, parental education, parental IQ, alcohol use during pregnancy, prepregnancy, weight, cesarean section, birth weight, colic, prenatal care, maternal smoking, current medication use by child, home environment, caretaker education, current caretaker marijuana use, and disruption in caregiving	Needleman, 1990: 0.16 Hair Pb: Marlowe, 1982: 0.41 Marlowe, 1985: 0.44 Marlowe, 1993: (0.48) Bone Pb: Needleman, 1996: 0.12 Needleman, 2002: 0.14 **All studies: *r* = 0.19 (95% CI 0.14, 0.23), *p* < 0.001** (Q test p < 0.001 indicating heterogeneity) **Excluding Hair: *r* = 0.15 (95% CI 0.11, 0.18), *p* < 0.001** (Q test p =0.31 improving homogeneity)	
Prospective McMichael (1994) Port Pirie, Australia *Population may overlap with Wigg (1988) and others*	262 children living in and around the Pb smelting town of Port Pirie, South Australia, followed since birth; re-evaluated at age 8. Year = 1979-1982 (at baseline). Male = 43.3%	Average age when teeth were shed: 6.8 (0.7) years	Cord blood Pb: 8.9 (0.3) µg/dL Tooth Pb (geometric mean, whole deciduous incisor): 8.6 (1.9) µg/g	Intellectual status at age 7: Wechsler Intelligence Scale for Children (WISC-R)	One-tailed variance ratio and Student's t tests (clear directional hypothesis) and 90% CIs Multiple regression model with final covariates: sex, birth weight, birth order, feeding style (breast, bottle, or mixed feeding), duration of breast feeding, parental smoking, mother's age at birth, period of residence in Port Pirie, SES, HOME score, mother's IQ, father's education, parents living together, and age the tooth was shed	Adjusted effect from an increase in tooth Pb from 3 to 22 µg/g: Estimate and 90% CI, one-tailed test *p* value Information: 0.6 (-0.6, 1.8), **p < 0.001** Similarities: 1.0 (-0.2, 2.3), **p < 0.001** Arithmetic: 1.1 (-0.1, 2.4), **p < 0.001** Vocabulary: 0.2 (0.8, 1.1), **p < 0.01** Comprehension: 0.4 (-0.7, 1.4), **p < 0.01** Picture Completion: 0.1 (-0.9, 1.0), *p* = 0.09 Picture Arrangement: 0.0 (-1.2, 1.3), *p* = 0.02 **Block Design: 2.5 (1.2, 3.8) p < 0.01** Object Assembly: 0.5 (-0.4, 1.4), *p* = 0.06 Coding: 0.1 (-1.1, 1.3), *p* = 0.49 Verbal IQ: 4.2 (-0.8, 9.1), **p = 0.01** Performance IQ: 4.5 (-0.8, 9.8), **p < 0.01** **Full-scale IQ: 5.1 (0.2, 10.0), p < 0.01** Partial regression coefficient per log unit tooth Pb: **Block Design: -1.25 points (90% CI -0.61, -1.89)** **Full-scale IQ: -2.55 points (90% CI -0.13, -4.9)**	Tooth Pb was significantly associated with decreased performance on full-scale IQ and block design test at age 7.
Cross-sectional Min (2007) Seoul, Korea	61 children aged 7-16 years; recruited during family health examination in	Mean not stated 7 to 16 years	Overall: 2.89 7-10 yrs (n=21): 2.73 (0.92)	Neurobehavioral function as measured by the Swedish	Linear regression Models included age, gender, and mother's	Multiple linear regression of neurobehavioral test and blood Pb: Pb Estimate (SE), *P*-value; R^2 **Simple reaction time: 16.80 (8.45), *P* =0.05; R^2=0.68** Digit span : -0.51 (0.29), *P* =0.08; R^2=0.46	Concurrent blood Pb was significantly associated with

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	Seoul, Korea. Year not stated Male = 54%		11-13 yrs: (n=24): 3.04 (0.75) 14-16 yrs (n=24): 2.74 (0.71)	performance evaluation system-Korean adaptation. Included: simple reaction time, symbol digit (measure of perceptual speed), digit span (short term memory capacity); finger tapping speed for dominant and non-dominant hands (maximum rate of repetitive movement).	neurobehavioral test performance.	Symbol digit: 147.72 (118.80),*P* =0.22; R^2=0.71 Finger tapping speed (dominant): -0.35 (1.43),*P* =0.81; R^2=0.55 Finger tapping speed (non-dominant): 0.44 (1.74), *P*=0.79; R^2=0.43	longer simple reaction time – an indicator of attention – in school age children.
Prospective Min (2009) Cleveland, OH	278 inner-city children from cohort study of prenatal cocaine; recruited at birth Year = 1994-1996 Male=48%	4,9, and 11	At age 4: 7(4.1)	Intelligence assessed using the abbreviated Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R) at 4 years and the entire Wechsler Intelligence Scales for Children-Fourth Edition (WISC-IV) at 9 and 11 years of age	Multiple regression analysis Adjustments differ by endpoint including HOME score, current caregiver's PPVT-R at 4 years, sex, parity, maternal marital status, and head circumference at birth, race, log of prenatal cocaine and alcohol average	<u>Regression of blood Pb at 4 (<5µg/dL vs ≥5µg/dL) and cognition:</u> adjusted mean decline at higher blood level <u>Tested at 4 years of age</u> Full Scale IQ 2.19 (p=0.23) **Performance 5.01(p=0.01)** <u>Tested at 9 years of age</u> Full Scale IQ 2.83 (p=0.11) Verbal comprehension 1.72 (p=0.32) **Perceptual reasoning 4.73 (p=0.01)** WJTA Math 3.02(p=0.06) **MJTA Reading 6.05 (p=0.003)** <u>Tested at11 years of age</u> Full Scale IQ 2.13(p=0.23) Verbal comprehension 1.8 (p=0.26) Perceptual reasoning 2.61 (p=0.16) Working memory 1.82 (p=0.41) WJTA Math 1.63 (p=0.37) **MJTA Reading 3.86 (p=0.04)** <u>Regression of blood Pb at 4 and cognition in all children:</u> coefficient (SE) <u>Tested at 4 years of age</u> **Full Scale IQ -0.50(0.20) (p≤0.05)** Verbal -0.20(0.190) **Performance -0.74(0.22)(p≤0.001)** <u>Tested at 9 years of age</u> **Full Scale IQ -0.41(0.19) (p≤0.05)** Verbal comprehension -.35(0.18) (p≤0.10) **Perceptual reasoning -0.45(0.21) (p≤0.05)**	Blood Pb at age 4 was significantly associated with decreased full scale IQ at age 4, 9 and 11; performance IQ at 4; perceptual reasoning and reading scores at age 9 and 11; and verbal comprehension and math scores at age 11.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Working memory -0.31(0.21) Processing speed –0.25(0.19) WJTA Math -0.33(0.18) (p≤0.10) **MJTA Reading –0.58(0.23) (p≤0.05)** Tested at11 years of age **Full Scale IQ -0.54(0.19) (p≤0.01)** **Verbal comprehension -.51(0.17) (p≤0.01)** **Perceptual reasoning -0.61(0.20) (p≤0.01)** Working memory -0.43(.24) (p≤0.10) Processing speed –0.24(0.20) **WJTA Math -0.45(0.20) (p≤0.05)** **MJTA Reading –0.60(0.21) (p≤0.01)**	
Cross-sectional (Minder *et al.* 1994) Netherlands	43 boys who attended special education schools in the Netherlands. Year not stated Male=100%	8 - 12 years	Hair Pb 1.26 ppm (1.09) **Lack of blood Pb measure limits the utility*	Attention measured by varied psychological tests including Eye-Hand Coordination, Simple Reaction Time, and Choice Reaction Time from the Neurobehavioral Evaluation System; Mazes, Digit Span, and Coding from the Wechsler Intelligence Scale for Children-Revised (WISC-R); Underlining Test (shortened version), Stroop Test, Trail Making Test A and B, Beery Test, and Dichotic Listening Test.	Correlation and multiple regression analysis Adjusted for age, SES, IQ, and pica	Correlation of hair Pb with test performance time: *r*, *p* **Simple Reaction Time: *r*=0.37, *p*=0.008** **Trail Making Test A: *r*=0.29, *p*=0.032** **Trail Making Test B: *r*=0.40, *p*=0.004** other tests p>0.05 Proportion of test score variance explained by Pb: **Simple Reaction Time:, 8.3, *p*=0.046** Trail Making Test A: 5.0, *p*=0.155 **Trail Making Test B: 11.7, *p*=0.022** **Trail Making Test B, reaction time correct.:9.9, *p*=0.037**	Hair Pb was significantly associated with slower reaction time and less flexibility in changing attention focus in children with learning problems.
Cross-sectional (Minder *et al.* 1998) Netherlands	313 boys who attended special education schools in the Netherlands. Year not stated Male=100%	9-12 years	4.4 (2.2) Range: 0.8-16.0	Cognition was assessed by extensive theory-based testing: the Simple Reaction Time task, Block Task compatible and incompatible, Digit Span forward and backward, Digit Span	Student's t-test, log transformed Socioeconomic status, thumb sucking and/or nail biting, and season	There were no significant correlations between blood PB and cognitive test results (data not shown). Blood Pb levels did not effect the final model when included as an independent variable or when forced to load on reaction time(n=267).	Blood Pb was not significantly correlated with any cognitive test in children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				sequence, Letter Span, Counting Span forward and backward, Trail Making Test A and B, Trail Making Test revised, Sternberg task, Brus reading Speed task, Raven task, and Bourdon-Vos task			
Retrospective cohort Miranda (2007) NC, USA *Population may overlap with Miranda (2009)*	8,603 4th grade children tested for reading and 8,627 tested for math at the North Carolina Education Research Data Center without a limited English proficiency and who were either black or white Year: 2000 – 2004 % male not stated	4th grade [age not reported, 4th grade is usually 9 – 10 years old]	5.19 µg/dL Pb screening data from the Childhood Lead Poisoning Prevent. Program in 1995-1998 (<5 years of age)	Educational achievement in 4th grade was measured by performance on state-required End of Grade (EOG) test results	Multivariate regression analysis Sex, race, school system, whether the school is a charter school, participation in the free or reduced-price lunch program, parental education, daily computer use, age at which blood Pb screen occurred.	Multivariate Regression model, 4th grade Reading EOG: **2 µg/dL Coefficient = -0.70; p=0.05** **4 µg/dL Coefficient = -1.77; p<0.0001** **6 µg/dL Coefficient = -2.33; p<0.0001** **8 µg/dL Coefficient = -2.66; p<0.0001** **≥10 µg/dL Coefficient = -2.92; p<0.0001** Multivariate Regression model, 4th grade Mathematics EOG: **2 µg/dL Coefficient = -0.71; p=0.03** **4 µg/dL Coefficient = -1.53; p<0.0001** **6 µg/dL Coefficient = -2.13; p<0.0001** **8 µg/dL Coefficient = -2.35; p<0.0001** **≥10 µg/dL Coefficient = -2.07; p<0.0001**	Blood Pb levels in early childhood (<5 years) are significantly associated with lower educational achievement in 4th grade (9-10 years) as measured by performance on end-of-grade testing.
Retrospective cohort Miranda (2009) NC, USA *Population may overlap with Miranda (2007)*	57,678 children from the North Carolina Childhood Lead Poisoning Prevention Program blood Pb surveillance registry linked to the North Carolina Education Research Data Center for all 100 counties in NC; self-reported as black or white without limited English proficiency; Year: 1995-1999 (Pb) and 2001-2005	Age range: 9-36 months when blood Pb measured Testing done in 4th grade [age not reported, 4th grade is usually 9 to 10 years old]	Mean: 4.8µg/dL Median: 4µg/dL Range: 1-16 Pb screening data from the Childhood Lead Poisoning Prevent. Program in 1995-1998	4th-grade reading scores from End of Grade (EOG) testing	Multivariate linear regression with EOG as the response variable and blood Pb level modeled using dummy variables for each blood Pb level Predictor variables: race, sex, parental education, free/reduced lunch program, and charter school (indicator of lower SES in NC)	Multivariate Regression of 4th-grade reading EOG score (ref: white, female, screened 9-18 months, Wake County Schools, no free/reduced lunch, parents HS graduates, blood Pb=1µg/dL) coeff. (95%CI), *p>t* **Pb=2µg/dl (dummy var.): -0.30 (-0.58, -0.01), 0.04** **Pb=3µg/dl (dummy var.): -0.46 (-0.73, -0.19), 0.00** **Pb=4µg/dl (dummy var.): -0.52 (-0.79, -0.24),0.00** **Pb=5µg/dl (dummy var.): -0.80 (-1.08, -0.51), 0.00** **Pb=6µg/dl (dummy var.): -0.99 (-1.29, -0.68), 0.00** **Pb=7µg/dl (dummy var.): -1.07 (-1.40, -0.74), 0.00** **Pb=8µg/dl (dummy var.): -1.35 (-1.73, -0.97), 0.00** **Pb=9µg/dl (dummy var.): -1.20 (-1.64,-0.75), 0.00** **Pb=10+µg/dl (dummy var.): -1.75 (-2.09, -1.41), 0.00** Screened 18-27 months: 0.36 (-0.10, 0.17), 0.61 **Screened 27-36 months: -0.61 (-0.78, -0.43), 0.00** **Black (1=black, 0=white): -3.55 (-3.71, -3.40), 0.00** **Male (1=Male, 0=female): -1.50 (-1.62, -1.38), 0.00** **Free/Reduced Lunch: -2.09 (-2.24, -1.94), 0.00**	Blood Pb levels in early childhood (<5 years) contribute to lower scores on reading tests at the end of the 4th-grade in a dose-dependent manner. Parental education and low SES are stronger predictors of test scores, but

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	(testing) % male not stated					**Parents with some HS: -2.78 (-3.01, -2.55), 0.00** **Parents with some post-HS: 2.00 (1.84, 2.15), 0.00** **Parents completed college: 4.94 (4.75, 5.12), 0.00** **Parents completed grad. school: 7.12 (6.77, 7.47), 0.00** **Charter schools: -2.58 (-3.06, -2.10), 0.00**	Pb shows an independent effect.
Cross-sectional Muldoon (1996) PA and MD, USA	530 elderly women from the Study of Osteoporotic Fractures (SOF), two clinics. Rural dwellers came from Monongahela Valley (PA) and urban dwellers came from the Baltimore clinic (MD); Year=1990-1991 Male=0%;	mean=70.5; no SD reported	Geometric mean: 4.8 (1.6)	Cognitive function assessed by neuropsychological tests of memory, language, visuospatial ability, and general intellectual status measured with Mini-Mental Status Examination, part B of the Trailmaking Test, the Digit Symbol substitution test from the Wechsler Adult Intelligence Scale-revised (WAIS-R), and an Incidental Memory test	Logistic regression analyses; analysis of variance; analysis of covariance <u>For Trailmaking, Digit Symbol, and Incidental Memory tests:</u> Age, education, and tobacco and alcohol consumption <u>For Reaction Time tests totals:</u> Age, tobacco and alcohol consumption, and history of diabetes and/or arthritis	Association of blood Pb levels(low ≤3µg/dL, medium 4-7µg/dL, and high >8µg/dL), and performance on neuropsychological test scores: Adj. OR (95% CI) Rural Monongahela Clinic: <u>Trailmaking</u> Low blood Pb: reference **Medium blood Pb: 2.05 (1.05,4.02)** **High blood Pb: 2.60 (1.04, 6.49)** Digit Symbol Substitution Low blood Pb: reference **Medium blood Pb: 2.03 (1.06, 3.88)** **High blood Pb: 3.73 (1.57, 8.84)** <u>Incidental Memory</u> Low blood Pb: reference Medium blood Pb: 1.37 (0.77, 2.41) High blood Pb: 1.89 (0.83, 3.41) <u>Reaction Time tests totals</u> Low blood Pb: reference Medium blood Pb: 1.37 (0.71, 2.65) High blood Pb: 1.16 (0.45, 3.01) Urban Baltimore Clinic <u>Trailmaking</u> Low blood Pb: reference Medium blood Pb: 0.97 (0.40, 2.40) High blood Pb: 0.79 (0.20, 3.04) <u>Digit Symbol Substitution</u> Low blood Pb: reference Medium blood Pb: 0.61 (0.25, 1.50) High blood Pb: 0.64 (0.16, 2.47) <u>Incidental Memory</u> Low blood Pb: reference Medium blood Pb: 0.50 (0.22, 1.16) High blood Pb: 0.99 (0.28, 3.49) <u>Reaction Time tests totals</u> Low blood Pb: reference Medium blood Pb: 0.61 (0.23, 1.58) High blood Pb: 1.07 (0.30, 3.84)	Blood Pb in elderly women was significantly associated with poorer cognitive performance on the Trailmaking and Digit Symbol Substitution tests in the rural population, but not in the urban population.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Cross-sectional Needleman (1979) MA, US *Population may overlap with (Needleman et al. 1990)*	58 children with high dentine levels and 100 children with low dentine Pb levels. Year=1975-1979 % male not stated	First and second grade	Dentine Pb levels: High: >24 ppm Low: <6 ppm	Wechsler Intelligence Scale for Children (Revised) (WISC-R);	Student t-test; analysis of covariance Mother's age at subject's birth, mother's educational level, father's socioeconomic status, number of pregnancies, and parental IQ	High vs. low dentine Pb and cognitive performance: **Full-scale IQ: p-value=0.03** Verbal IQ: p-value=0.06 Performance IQ: p-value=0.13 **Seashore Rhythm Test: p-value=0.002** Token Test: p-value=0.09 **Sentence-Repetition Test: p-value=0.04**	Children with high dentin Pb levels scored significantly lower on the Full Scale IQ, the Seashore Rhythm Test, and the Sentence-Repetition Test.
Prospective (Needleman *et al.* 1990) MA, US *Population may overlap with (Needleman et al. 1979)*	132 adolescents who had been studied as primary school-children in 1975-1978 were reexamined in 1988. Year= 1988 Male=55.3%	18.4 years	Tooth (dentin) Pb Median=8.2 ppm Range: <5.9 to >22.2 ppm	Neurobehavioral deficits and academic achievement in high school and shortly following graduation where measured by a battery of tests from the Neurobehavioral Evaluation System.	Multiple regression analysis Mother's age at time of subject's birth, mother's educational level, mother's IQ, family size, socioeconomic status, sex, age at time of testing, birth order, alcohol use, and whether the subject and the mother left the hospital at the same time	Dentine Pb levels >20ppm vs <10 ppm AdjOR (95% CI) **Diminished academic success: 7.4 (1.4, 40.8)** **Reading disability: 5.8 (1.7, 19.7)** Multiple regression analysis of academic achievement deficits. Dentin Pb levels >20 ppm vs. <10ppm **Highest grade achieved: β(SE)=-0.027(0.01); p=0.013** **Reading grade equivalent: β(SE)=-0.072(0.02);p=0.001** **Class standing: β(SE)=-0.006(0.003); P=0.048** **Absenteeism: β(SE)=4.73 (1.8); p=0.01** **Grammatical reasoning: 0.178(0.068); p=0.011** **Vocabulary: -0.122(0.033); p=0.001** **Minor antisocial behavior: -0.739(0.035); p=0.038**	Dentin Pb was significantly associated with academic achievement deficits and self-reports of delinquent activity in young adulthood.
Meta-analysis Needleman (1990)	Meta-analysis of 12 studies of Pb and childhood IQ: 7 with blood Pb (Yule (1981), Lansdown (1986), Ernhart (1985), Schroeder (1985), Hawk (1986), Fulton (1987), and Hatzakis (1987)) and 5 with tooth Pb (Winneke (1983), Needleman (1985), Fergusson (1988a), Pocock (1987), and Hansen (1989)).	Ranged from preschool to age 12 years	<u>Blood Pb (µg/dL)</u> Yule, 1981: 13 Lansdown, 1986: 13 Ernhart, 1985: >30 Schroeder, 1985: 30 Hawk, 1986: 21 Fulton, 1987: 11.5 Hatzakis, 1987: 23 <u>Tooth Pb (ppm)</u> Winneke, 1983: 6.2 Needleman, '85: 12.7 Fergusson, 1988: 6.2 Pocock, 1987: 5.1 Hansen, 1987: 10.7	Children's IQ	Multiple regression analysis Within group P values compared for homogeneity using the Rosenthal technique. Joint p-values and averaged effect sizes calculated using two different methods (Fisher and Mosteller). Correlations were converted to z-scores and weighted averages	Final adjusted model for Pb in each study: *r* (SE), *P* <u>Blood Pb</u> **Yule, 1981 (n=129): -8.08 (4.63), *P* = 0.04** Lansdown, 1986 (n=86): 2.15 (4.48), *P* = 0.68 Ernhart, 1985 (n=80): NA, estimated from data ***P* = 0.04** **Schroeder, 1985 (n=104): -0.199 (0.07), *P* = 0.003** **Hawk, 1986 (n=75): -0.255 (0.15), *P* = 0.05** **Fulton, 1987 (n=501): -3.70 (1.31), *P* = 0.003** **Hatzakis, 1987 (n=509): -0.266 (0.07), *P* = 0.001** **ALL: z=-5.46, *P* < 0.001; weighted *r* = -0.152 (-0.2, -0.1)** <u>Tooth Pb</u> Winneke, 1983 (n=115): -0.125 (4.66), *P* = 0.49 **Needleman, 1985 (n=218): -0.21 (0.07), P = 0.001** Fergusson, 1988 (n=724): -1.46 (1.25), *P* =0.12 Pocock, 1987 (n=388): -0.77 (0.63), *P* = 0.11 **Hansen, 1989 (n=156): -4.27 (1.91), *P* = 0.01** **ALL: z=-2.65, *P* = 0.004; weighted *r* = -0.08 (-0.13, -0.03)**	Blood and tooth Pb were significantly associated with decreases in children's IQ in a meta-analysis of 12 studies.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
					were sued to construct estimates and 95% CIs.	Sensitivity analysis showed that no single study was responsible for the significance of the final findings. The authors concluded that the hypothesis that Pb lowers children's IQ at relatively low dose is strongly supported.	
Retrospective Needleman (1996) Pittsburgh, PA, USA	212 boys from a cohort of students enrolled in the Pittsburgh Youth Study (PYS), boys in the low-Pb group were matched to boys in the high-Pb group; Year not stated Male=100%	12.4 (0.72)	Bone Pb (µg/g) measured at 12 years of age: mean not reported	Child Behavior Checklist (CBCL): teachers' and parents' reports given at ages 7 and 11; subjects' self-reported anti-social behavior scale (SRA) given at subjects mean age of 7.4 years, the Self-reported Delinquency scale (SRD) at subjects mean age of 10.9 years	Analysis of covariates (ANCOVA) Mother's intelligence quotient (Raven's score), mother's highest grade achieved, mother's age at child birth, both parents present in the home, child's age, caregiver's job code, number of siblings, race, and child's health status	Association between bone Pb at age 12 and CBCL Scores OR (95% CI): <u>Attention:</u> **Parent: 19.35 (8.9, 41.6)** Teacher: 1.71 (0.57, 5.1) <u>Delinquency</u> Parent: 1.89 (0.83, 4.3) Teacher: 2.16 (0.96, 4.6) <u>Aggression:</u> Parent: 1.49 (0.45, 4.9) **Teacher: 2.18 (1.03, 4.6)** At 11 years of age, parents reported significant Pb related association with the following CBCL clusters scores: somatic complaints and delinquent, aggressive, internalizing, and externalizing behavior. Teachers reported significant associations of Pb with somatic complaints, anxious/depressed behavior, social problems, attention problems, and delinquent, aggressive, internalizing, and externalizing behavior. CBCL scores were more likely to worsen between 7 and 11 years of age in high-Pb subjects vs. low-Pb subjects Low-Pb group: scored > 30th percentile on the self-reported anti-social scale High-Pb group: scored <70th percentile on the self-reported anti-social scale	Bone Pb at age 12 was significantly associated with increased attention and aggression at age 12, and several self-reported measures of antisocial (age 7.4) and delinquent behavior (age 10.9). The authors suggest that the effect follows a developmental course.
Case-control Needleman (2002) PA, USA	Cases: 194 youths adjudicated as delinquent by the Juvenile Court; Controls: 146 non-delinquent youths from the same high schools Year=1996 – 1998 % male not stated	Range: 12-18 years	Tibia bone Pb (ppm) Cases: 11.0 (32.7) Controls: 1.5 (32.1)	Delinquents (cases) were youths arrested and adjudicated by the Juvenile Court as delinquent	Logistic regression Race, parents' education and occupation, presence of two parental figures in the home, number of children in the home, neighborhood crime rate.	Odds ratio for delinquency by tibia bone Pb All subjects: **AdjOR (95% CI)=3.7 (1.3, 10.5)** Whites: **AdjOR (95% CI)=3.8 (1.1, 13.3)** African Americans: **AdjOR (95% CI)=2.2 (0.5, 10.0)**	Tibia bone Pb was significantly associated with delinquency (arrest and adjudication) in white and African-American youth (age 12-18).

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Cross sectional Nicolescu (2010) Romania	83 children 8 to 12 years old from Bucharest (n=37) and Pantelimon (n=46) without symptoms Year = 2006-2007 % male not stated	9.9 (SD not reported)	Bucharest: 3.2 Pantelimon:5.1 (SDs not reported) Median (1%, 99%) for both towns: 3.7 (1.1, 14.2)	Neurobehavioral measures of attention with 4 (of 7) attention tasks from the ADHD-tailored German KiTAP-battery and behavioral ratings from parents and teachers: ICD-10 (hyperactivity), DSM-IV (attention deficit), and the foreign assessment for attention deficit/hyperactivity disorders in Romanian *Blood Hg and Al also measured*	Multiple linear regression Adjusted for town, gender, age, computer experience, handedness, eye problems, number of siblings, parental education, maternal smoking during pregnancy, maternal alcohol during pregnancy, and family psychopathology	<u>KiTAP performance correlation with blood Pb</u> Response Time Alertness:0.14 **Errors, Alertness: 0.25, *p* < 0.05** Response Time Go-No-Go: 0.21 **False Alarm Rate Go-No-Go: 0.33, *p* < 0.01** Response Time Distractibility:-0.02 **False Alarm Rate Distractibility 0.23, *p* < 0.05** **Response Time Flexibility: 0.31, *p* < 0.01** **False Alarm Rate Flexibility: 0.45, *p* < 0.01** <u>ADHD correlation with blood Pb: Parents/Teachers</u> **Inattention: 0.32, p < 0.01/0.26, p < 0.05** Hyperactivity: **0.30, p < 0.01**/0.12 Impulsivity: **0.33, p < 0.01**/ 0.15 **ADHD-total: 0.33, p < 0.01/0.22, p < 0.05** <u>Adjusted Change in KiTAP False Alarm Rate with a doubling of blood Pb</u>: % change (95% CI), *p* value Alertness: 14 (-13, 58), *p* > 0.10 Go-No-Go: 28 (-0.05, 72), *p* = 0.09 **Distractibility: 35(-0.01, 84), *p* = 0.05** Flexibility: 28% (-10, 84), *p* > 0.10 There were no increases with Response Time <u>Adjusted Change in Parental ADHD with a doubling of blood Pb:</u> % change (95% CI), *p* value Inattention: 4, (-12, 23), *p* > 0.10 Hyperactivity: 17(-0.02, 41), *p* = 0.08 **Impulsivity: 23(-0.01, 52), *p* = 0.05** ADHD total: 11 (-0.06, 29, *p* > 0.10 <u>Adjusted Change in Teacher's ADHD with a doubling of blood Pb:</u> % change (95% CI), *p* value Inattention: 14 (-0.05, 36), *p* > 0.10 Hyperactivity: 14 (-0.07, 39), *p* > 0.10 Impulsivity: 21 (-0.04, 52), *p* = 0.09 ADHD total: 16 (-0.02, 37), *p* = 0.08 Restriction to children with blood Pb <10 µg/dl had only a marginal influence on outcome (data not shown). *Hg and Al were not associated*	Blood Pb levels were associated with ADHD-related behaviors in children from 8-12 years of age.
Case-control Nigg (2008) USA *Population may overlap with Nigg (2010)*	150 children participated (47 with ADHD Predominantly Inattentive type, 50 with ADHD-Combined type, and 53 control subjects)	14 years Range 8-17 years	<u>Child blood Pb</u> 1.03 (SE 0.04) µg/dL Range 0.40-3.47 <u>Maternal blood Pb</u> (at the time of assessment): mean not stated	Attention-deficit/hyperactivity disorder (ADHD) measured with the Child Behavior Checklist (CBCL), Conners Rating Scale-Revised (CRS),	Pearson Correlation Gender, family income, age	<u>Unadjusted blood Pb and ADHD diagnosis</u>: mean (SD) ADHD-PI: 0.95 (0.46) ADHD-C: 1.26 (0.67) Control: 0.89 (0.39) **p-value=<0.01** <u>Pearson Correlations of Blood Pb with Behavioral Measures</u>: Child Pb; Maternal Pb **Child Estimated FSIQ: C -0.18, p<0.05;** M 0.10;	Concurrent blood Pb levels were statistically significantly higher in ADHD-combined type

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	Year not stated % Male: Controls=60%, ADHD-PI=49% ADHD-C=80%		Range 0-5.3 Correlation with child blood Pb: r = 0.16, p = 0.053	and the ADHD Rating Scale; Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-E); Wechsler Intelligence Scales for Children-4th Edition (WISC-IV); Wechsler Individual Achievement Test-2nd Edition (WIAT-II); Cognitive control assessed by Stop task ADHD diagnosed independently by two licensed clinicians.		**DSM-IV Inattention: C 0.18, p<0.05;** M -0.10; Not significant after adj for income and gender **DSM-IV Hyperactivity: C 0.31, p<0.01;** M 0.03; **After adj for income and gender, p<0.05** **After adj for Inattention: *β* = 0.19, p=0.001** **DSM-IV ADHD: C 0.24, p<0.01;** M -0.10; DSM-IV Conduct Disorder: C 0.02; **M 0.21, p<0.05;** CRS Cognitive Problems: C 0.14; M -0.10; **CRS Hyperactivity: C 0.25, p<0.01;** M -0.10; **CRS Oppositional: C 0.18, p<0.05;** M -0.06; **CRS ADHD Index: C 0.17, p<0.05;** M -0.06; **CBCL Attention Problems: C 0.21, p<0.05;** M -0.09; The authors use path models to show blood Pb levels were linked with a lower IQ (p<0.05), but that IQ did not account for effects on hyperactivity. Instead, they state that hyperactivity mediated effects of Pb on IQ. This effect was independent of effects of Pb on IQ. The also show that cognitive control mediates the effect of blood Pb on ADHD hyperactive-impulsive symptoms with income, gender, and age covaried.	than in non-ADHD control children. Blood Pb was significantly correlated with hyperactivity-impulsivity after controlling for covariates. Blood Pb was also significantly associated with lower IQ scores, but IQ did not account for the effects on hyperactivity.
Case-control Nigg (2010) USA *Population may overlap with Nigg (2008)*	236 children participated (61 ADHD-Combined type, 47 ADHD Predominantly Inattentive type, 99 non-ADHD control, 29 unclassified borderline, situational or not otherwise specified cases). There were 78 sibling pairs (n=156 siblings) Year= % Male: Control-43%; NOS=48%; ADHD-PI=68%; ADHD-C=74%	6-17 years	Child unadj. Blood Pb: Control= 0.20 (0.30) NOS=0.78 (0.24) ADHD-PI=0.72 (0.35) ADHD-C=0.88 (0.44) All: 0.73 (0.04)	ADHD diagnosed by a semi-structured clinical interview (Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-E) completed by parents; ADHD rating scale and Conners ADHD Rating Scale completed by parents and teachers; IQ measured by WISC-IV; academic achievement estimated by WIAT-2; behavior disorders measured by DSM-IV	Regression models Household income, maternal smoking, child age, child sex, child hemoglobin level; IQ	<u>Regression of child blood Pb with parent-reported ADHD symptoms</u>: standardized results, parameter (SE) <u>KSADS Lifetime</u> Inattention: 0.11(0.07); NS **Hyp-Imp: 0.18 (0.06); p<0.001** <u>Conners</u> **Cognitive: 0.20 (0.07); p<0.01** **Hyp-Imp: 0.25 (0.07); p<0.001** <u>Regression of child blood Pb with teacher behavior ratings</u>: standardized results, parameter estimates (SE) <u>ADHD Rating Scale</u> Inattention: 0.06 (0.06); NS Hyp-Imp: 0.09 (0.06) ; NS <u>Conners</u> **Cognitive: 0.15 (0.06); p<0.05** Hyp-Imp: 0.11 (0.06); NS	Concurrent blood Pb was significantly associated with parent and teacher reported Conners cognitive impairments and reports of hyperactive-impulsiveness by parents in children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Nordberg (2000) Stockholm, Sweden	762 participants of the Kungsholmen Project registered in 1987; Years (follow-up)= 1994-1996; Male=23%	87.3 (4.9) (all ≥75 years)	3.7 (2.3) Men = 4.6 Women = 3.5	Cognitive function measured on the Mini-Mental State Examination (MMSE)	Student's t-test; Chi-squared test; multiple regression	No relationship was found between Pb concentrations and MMSE [data not reported]	Pb blood levels were not significantly associated with cognitive function (by MMSE) in elderly people.
Prospective nested case-control Opler (2004, 2005) Oakland, CA, USA *Population may overlap with Opler (2008)*	44 cases (with schizophrenia) and 75 matched controls from a cohort of live births in the Prenatal Determinants of Schizophrenia (PDS) study; Years: enrolled 1959-1967 % male not stated	mean not reported 15 - 22 years	Dichotomized maternal blood Pb in the 2nd trimester (≥ 15 or <15, estimated from δ -ALA ≥9.05 ng/ml)	Schizophrenia (includes schizophrenia, schizoaffective disorder schizophrenia, schizotypal personality disorder, delusional disorder, and nonaffective psychoses not otherwise specified)	Logistic regression Maternal age	Odds ratios for schizophrenia associated with 15 µg/dL blood Pb (estimated from delta-ALA≥9.05) by conditional logistic regression: Adj. OR (95 %CI)= 2.43 (0.99, 5.96), p =0.051	Maternal blood Pb ≥15 µg/dL in the 2nd trimester was significantly associated with a greater odds ratio for schizophrenia at borderline significance (p=0.51) in 15-22 year old children.
Pooled prospective nested case-control Opler (2008) Oakland, CA; Providence, RI; and Boston, MA, USA *Population may overlap with Opler (2004, 2005)*	71 cases (with schizophrenia) and 129 matched controls (44 cases and 75 controls from the Prenatal Determinants of Schizophrenia (PDS) study and 27 cases and 54 controls from the New England cohort of the National Collaborative Perinatal Project (NE-NCPP);Year= 1959-1966 and 1969-1967; % male not stated	Not stated	Dichotomized to maternal blood Pb in 2nd trimester of ≥ 15 or <15 (estimated from δ -ALA)	Schizophrenia (includes schizophrenia, schizoaffective disorder schizophrenia, schizotypal personality disorder, delusional disorder, and nonaffective psychoses not otherwise specified)	Multilevel random-intercept logistic regression Maternal age and maternal education	Odds ratios for schizophrenia associated with 15 µg/dL blood Pb (estimated from delta-ALA≥9.05) in PDS and NE-NCPP: Conditional logistic regression: **Adj.OR (95% CI)= 2.17 (1.12-4.17), p-value=0.020** Random intercept logistic regression: **Adj.OR (95% CI)= 1.92 (1.05-3.52), p=0.035**	Maternal blood Pb ≥15 µg/dL in the 2nd trimester was significantly associated with a greater odds ratio for schizophrenia in 15-22 year old children.
Cross-sectional Osman (1999)	155 children from three towns in the	8.1 (2.1); Range: 4-14	Median: 7.2 Range: 1.9-28.1	Hearing was measured by	Multiple linear regression	Blood Pb and right and left hearing thresholds at different frequencies (covariates in model): *B* (95% CI)	Concurrent blood Pb was

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Poland	Katowice region - an industrial area in Poland, selected from the Katowice Lead Monitoring Programme cohort and the town of Bytom. Year not stated Males=52%		Children were selected based on blood Pb measured 1-3 years prior to current study (with a new blood Pb measure). 120 (42%) over 15µg/dL and 92 (33%) below 5µg/dL were invited to participate. 54% chose to participate.	audiologic tests (screening tympanometry) and BAEPs recording	Age, gender, Apgar score, ears without pathologies at inspection, nasopharynx without pathologies at inspection, ear diseases, frequent colds, mumps, gentamycin, environmental noise, and maternal smoking during pregnancy	Right ear: **0.5 kHz (age): 0.054 (0.035, 0.074)** **1 kHz (age, Apgar): 0.044 (0.026, 0.062)** **2 kHz (age, Apgar): 0.048 (0.029, 0.066)** **4 kHz (Apgar): 0.060 (0.039, 0.081)** **6 kHz(Apgar): 0.068 (0.044, 0.092)** **9 kHz(Apgar): 0.072 (0.050, 0.094)** Left ear: **0.5 kHz (age): 0.051 (0.026, 0.075)** **1 kHz (Apgar, gentamycin): 0.032 (0.014, 0.050)** **2 kHz (Apgar): 0.036 (0.019, 0.053)** **4 kHz (Apgar): 0.039 (0.020, 0.059)** **6 kHz (Apgar, no ear pathol.): 0.026 (0.004, 0.049)** **8 kHz (Apgar): 0.047 (0.024, 0.070)** No significant associations between BAEPs latencies in the whole study group (data not shown, except below). After adjusting for age, the effect of Pb for latency of wave I: B=0.057 (0.016-0.098), *P* = 0.052	significantly associated with increased hearing thresholds in children at all frequencies tested.
Prospective and cross-sectional Otto (1985) NC, USA	49 children (48 from low-income black families considered to be at risk for Pb poisoning) evaluated and followed up for 5 years. Baseline Year = 1977-1978 Male=53%	6-12 years	Baseline mean: 28 range 6-59 Current (5 years after baseline) mean: 14 range: 6-30 Correlation of baseline and current blood Pb = 0.74	Sensory function tests: slow wave voltage measured during passive sensory conditioning, active sensory conditioning, electro-encephalograph/electro-oculograph, brainstem auditory evoked potential (BAEP), Pattern-reversal evoked potentials for neurological assessment of visual system.	Multivariate regression Age, SES, gender, maternal IQ, and HOME	<u>Regression of baseline blood Pb and slow wave voltage during passive conditioning:</u> Pb quadratic: *F* = 1.18 (3,41df), *P* = 0.33 Current blood Pb was not associated <u>Regression of current blood Pb and slow wave voltage during active conditioning</u>: **Multivariate: *F* = 2.85 (6,39df), *P* = 0.02** Univariate: Frontal Cortex (500-1000msec): *P* = 0.15 Central Cortex (500-1000msec): *P* = 0.37 Parietal Cortex (500-1000msec): *P* = 0.71 **Frontal Cortex (1000-1500msec): *P*=0.025, r^2=0.11** **Central Cortex (1000-1500msec): *P*=0.046, r^2=0.09** **Parietal Cortex (1000-1500msec): *P*=0.002*, r^2=0.20** (*SES and maternal IQ kept in model) Baseline blood Pb was only significant at Parietal Cortex, 1000-1500msec (data not shown) <u>Regression of baseline blood Pb and BAEP latencies:</u> Multivariate: *F* = 2.32 (3,41df), *P* = 0.09 Univariate: Wave I: *F* = 2.15 (3,51df), *P* = 0.15 **Wave III: *F* = 9.06 (1,41df), *P* = 0.004*** (*sex kept in model) **Wave V: *F* = 8.67 (1,41df), *P* = 0.005**** (**sex and HOME kept in model) IPL V-1: *F* = 1.29 (1,42df), *P* = 0.26* (*sex kept in model)	Concurrent blood Pb was significantly associated with increased slow wave negativity during active conditioning but not during passive conditioning. Prior blood Pb, but not current blood Pb, was significantly associated with brainstem auditory evoked potential - suggestive of subclinical pathology of the auditory pathway. Significant associations

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						IPL V-III: *F* = 0.14 (1,43df), *P* = 0.71 IPL III-I: *F* = 2.16 (1,44df), *P* = 0.15 Current blood Pb was not associated with BAEP latencies (data not shown) <u>Regression of baseline blood Pb and pattern-reversal visual evoked potential latencies and amplitude:</u> Multivariate: *F* = 1.87 (3,39df), *P* = 0.15 Univariate: N1 latency: *F* = 0.09 (1,41df), *P* = 0.77 P1 latency: *F* = 1.03 (1,41df), *P* = 0.32 **N2 latency: *F* = 5.65 (1,41df), *P* = 0.022** **N1P1 amplitude: *F* = 7.22 (1,40df), *P* = 0.01*** (*SES kept in model) Current blood Pb had similar results, except N2 latency was not associated (data not shown). The significant associations were not in the predicted direction.	between concurrent and prior blood Pb with visual evoked potentials were not in the predicted direction.
Cross-sectional Park (2010) Boston, MA, USA *Population may overlap with Payton (1998) and others*	448 men from the Normative Aging Study Year= 1993-1996; (initially enrolled in 1963) Male= 100%	At bone Pb measurement: 64.9 (7.3) At first audiometric test: 42.5 (8.4)	Tibia Pb (µg/g): 22.5 (14.2) Patella Pb (µg/g): 32.5 (20.4)	Age-related hearing loss measured by hearing threshold examination at frequencies (kHz) 0.25, 0.5, 1, 2, 3, 4, 6 and 8.	Linear model (cross-sectional) and linear mixed effects model (longitudinal) Full adjustment included age, race, education, BMI, pack-years of cigarettes, diabetes, hypertension, occupational noise, and noise notch	<u>Adjusted effects estimates in hearing threshold (dB HL) with one IQR increase in bone Pb</u>: Estimate (95% CI) Tibia Pb (n=448; IQR = 15µg/g) 0.25 kHz: 0.42 (-0.38, 1.21) 0.5 kHz: 0.07 (-0.68, 0.82) 1 kHz: 0.22 (-0.65, 1.10) 2 kHz: 1.10 (-0.43, 2.62) 3 kHz: 1.17 (-0.72, 3.06) **4 kHz: 2.18 (0.13, 4.23), *p* < 0.05** 6 kHz: 1.71 (-0.28, 3.71) 8 kHz: 1.75 (-0.35, 3.86) Pure Tone Average (PTA): 0.83 (-0.18, 1.83) Patella Pb (n=447; IQR = 21µg/g) 0.25 kHz: 0.56 (-0.21, 1.33) 0.5 kHz: 0.50 (-0.23, 1.23) 1 kHz: 0.80 (-0.05, 1.64) **2 kHz: 1.81 (0.34, 3.28), *p* < 0.05** **3 kHz: 2.32 (0.50, 4.15), *p* < 0.05** **4 kHz: 3.43 (1.46, 5.41), *p* < 0.001** **6 kHz: 2.54 (0.61, 4.47), *p* < 0.05** **8 kHz: 2.65 (0.61, 4.68), *p* < 0.05** **Pure Tone Average (PTA): 1.58 (0.62, 2.55), *p* < 0.01** <u>Adjusted odds ratios in air conduction PTA hearing loss for a one IQR increase in bone Pb</u>: AdjOR (95% CI) Tibia Pb: 1.19 (0.92, 1.53) **Patella Pb: 1.48 (1.14, 1.91)** <u>Longitudinal adjusted effects estimates from hearing thresholds with a 1 IQR increase in tibia Pb for a time x</u>	Patella Pb was significantly associated with poorer hearing thresholds and age-related hearing loss, while tibia Pb was not. In longitudinal analyses, tibia Pb was significantly associated with the rate change in hearing thresholds at 1, 2, and 8Hz.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						tibia interaction term: β (SE) 0.25 kHz: 0.026 (0.018) 0.5 kHz: 0.026 (0.018) **1 kHz: 0.038 (0.017), $p < 0.05$** **2 kHz: 0.082 (0.026), $p < 0.01$** 3 kHz: 0.045 (0.030) 4 kHz: 0.049 (0.026) 6 kHz: 0.058 (0.003) **8 kHz: 0.090 (0.035), $p < 0.05$** **Pure Tone Average (PTA): 0.050 (0.017), $p < 0.01$** Time alone was significantly associated with hearing loss at all frequencies (all $p < 0.001$) and tibia Pb alone was not associated at any frequency (all $p > 0.05$).	
Prospective Payton (1998) Boston, MA, USA *Population may overlap with Wright (2003) and others*	141 middle-aged to elderly men from the Normative Aging Study (NAS); Year= 1993-1994 (initially enrolled in 1963) Male=100%	66.8 (6.8)	Blood Pb: 5.5 (3.5) Patella Pb (µg/g): 31.7 (19.2) Tibia Pb (µg/g): 22.5 (12.2)	Cognitive tests: Neurobehavioral Evaluation System (NES2) measuring continuous performance, and pattern comparison, pattern memory; the Wechsler Adult Intelligence Scale-Revised (WAIS-R) measuring digit span and backward, vocabulary; the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) measuring word list memory, constructional praxis, Boston naming test, and verbal fluency	Backwards-elimination multivariate linear regression; Pearson correlation coefficients; smooth plots Age, education	Regression models of cognitive outcomes in relation to blood, tibia, and patella Pb β(SE): Continuous performance (sustained attention) (ms): Blood Pb: 0.256 (1.393); p=0.90 Tibia Pb: -0.381 (0.416); p=0.40 Patella Pb: -0.475 (0.258); p=0.07 Pattern Comparison (perceptual speed) (s): **Blood Pb: 0.074 (0.032); p=0.020** Tibia Pb: 0.011 (0.010); p=0.30 Patella Pb: 0.005 (0.006);p=0.50 Pattern comparison (perceptual speed) (total # correct): Blood Pb: 0.012 (0.032); p=0.70 Tibia Pb: 0.014 (0.010); p=0.20 Patella Pb: 0.004 (0.006); p=0.10 Pattern Memory (immediate visual memory) (s): Blood Pb: .062 (0.037); p=0.10 Tibia Pb: 0.021 (0.011); p=0.053 Patella Pb: 0.011 (0.007); p=0.10 Pattern Memory (immediate visual memory) (total # correct): Blood Pb: -0.054 (0.073); p=0.50 Tibia Pb: 0.022 (0.023); p=0.30 Patella Pb: 0.018 (0.014); p=0.20 Digital Span Backward (auditory working memory) (total#): Blood Pb: -0.036 (0.054); p=0.50 Tibia Pb: 0.015 (0.016); p=0.40 Patella Pb: 0.010 (0.010); p=0.30 Vocabulary (verbal ability) (total #): **Blood Pb: -0.841 (0.200); p=0.0001** Tibia Pb: -0.030 (0.067); p=0.70 Patella Pb: -0.041 (0.039); p=0.30	Blood Pb was significantly associated with slower pattern comparison speed, and a deficit in vocabulary, word list memory, spatial ability and verbal ability. Tibia Pb was significantly associated with a deficit in spatial ability.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (μg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Word List Memory (immediate verbal memory) (total #): **Blood Pb: -0.182 (0.086); p=0.036** Tibia Pb: -0.003 (0.028); p=0.90 Patella Pb: -0.008 (0.017); p=0.60 Constructional praxis (spatial ability) (total #): **Blood Pb: -0.105 (0.039); p=0.008** **Tibia Pb: -0.031 (0.012); p=0.010** Patella Pb: -0.015 (0.007); p=0.053 Boston Naming Test (verbal ability) (total #): **Blood Pb: -0.036 (0.016); p=0.028** Tibia Pb: 0.0002 (0.005); p=1.0 Patella Pb: -0.002 (0.003); p=0.50 Verbal Fluency Test (verbal ability) (total #): Blood Pb: -0.203 (0.120); p=0.09 Tibia Pb: -0.011 (0.039); p=0.80 Patella Pb: -0.005 (0.024); p=0.80	
Cross-sectional Peters (2010) Boston, MA, USA *Population may overlap with Payton (1998) and others*	811 men in the Normative Aging Study; Year=1993-1997; (initially enrolled in 1963) Male = 100%	67.9 (6.99)	Blood : 5.07(.76) Patella (μg/g) 29.8(18.7) Tibia (μg/g) 21.3(13.2) Measured when outcome assessed	Cognitive assessment (Mini-Mental State Examination-MMSE), stress (health and behavior questionnaire and Perceived Stress Scale-PSS)	Multivariable regression Age, education, computer experience, English as a first language, smoking, and alcohol intake	Multiple regression of modifying potential of high stress on relationship of log-Pb and MMSE scores β (95%CI): **Blood Pb β=-0.57 (–0.90,-0.24) (p < 0.05)** **p=0.02 for stress interaction** Patella Pb β=-0.19 (–0.44,0.06) (p>0.05) p=0.06 for stress interaction Tibia Pb β=-0.14 (–0.38,0.10) (p>0.05) p=0.29 for stress interaction. **High Pb (above median blood, patella, or tibia Pb) and or high PSS scores were associated with a 0.05–0.08 reduction on the MMSE for each year of age compared with those with low Pb levels and PSS scores (*p* < 0.05).**	Blood Pb was significantly associated with deceased cognition in older men with higher stress. Although bone Pb alone was not significantly associated with cognition, high stress and blood or bone Pb modify the association between age and cognition.
Prospective Pilsner (2010) Mexico City, Mexico *Population may overlap with Gomaa (2002) and others*	255 mother-child pairs from the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) sequential birth cohort recruited	Mothers: 24.6 (5.1) years Children: Pb measured at birth and MDI at 24 months	Maternal bone Pb (1 month postpartum) Tibia: 10.5 (10.4)μg/g Patella: 14.7 (13.7)μg/g Cord blood: 6.7 (3.6)μg/dL	Bayley Mental Development Index at age 24 months (MDI-24) scores *Also studied MTHFR C677T (rs1801133) and A1298C (rs1801131)*	Multiple regression model Adjusted for maternal age, gestational age, maternal IQ, parity, low folate status, and marital status	Maternal MTHFR genotype was related to MDI-24 score, but there was no significant interaction with Pb exposure. *[Maternal bone and child cord blood Pb previously shown to be associated with MDI-24 in Gomaa (2002)]*	*MTHFR* genotype does not significantly modify a previously reported associations of maternal bone and child cord

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	from 3 low to moderate income hospitals; Year: 1994–1995 Male =			*genotype*			blood Pb with child neuro-development.
Meta-analysis; Pocock (1994)	Meta-analysis of 19 studies of Pb and children's IQ since 1979: 5 prospective (Baghurst (1992), Dietrich (1993b), Ernhart (1985), Cooney (1991), and Bellinger (1992)) and 9 cross-sectional blood Pb (Hatzakis (1987), Fulton (1987), Winneke (1990), Silva (1988), Lansdown (1986), Harvey (1988), Wang (1989), Yule (1981), and Winneke (1985)), and 7 cross-sectional tooth Pb (Fergusson (1988a), Smith (1983), McMichael (1994), Fulton (1989), Needleman (1979), Winneke (1983), and Bergomi (1989)).	Children age 5 or more	<u>Pros. Blood Pb (at 2)</u>: Baghurst, 1992: 21.2 Dietrich, 1993: 17.5 Ernhart, 1985: 16.7 Cooney, 1991: 14.2 Bellinger, 1992: 6.8 <u>Cross-Sect blood Pb</u>: Hatzakis, 1987: 23.7 Fulton, 1987: 11.5 Winneke, 1990: Bucharest: 18.9 Budapest: 18.2 Moden:11.0 Sofia:18.2 Dusseldorf, @6: 8.3 Dusseldorf, @8: 7.4 Silva, 1988: 11.1 Lansdown, '86: 12.9 Harvey, 1988: 12.3 Wang, 1989: 21.1 Yule, 1981: 13.5 Winneke, 1985: 8.2 <u>Cross-Sect tooth Pb (µg/g)</u>: Fergusson, 1988: ~6 Smith, 1983: 5.1 McMichael, '94: 8.6 Fulton, 1989: 9.3 Needleman, '79: 12.7 Winneke, '83: 6.2 Bergomi, 1989: 6.1	Children's IQ assessed by the Wechsler intelligence scale for children-revised (WISC-R), Wechsler preschool and primary scale of intelligence (WPPSI), the British ability scale	Multiple regression of full scale IQ on Pb (some original data obtained from study authors to allow comparison) The fixed effect method of Thompson and Pocock (1992) was employed.	Estimated change in IQ (SE) for an increase from 10 to 20 µg/dL blood Pb or 5 to 10µg/g tooth Pb: <u>Prospective, Blood</u>: Adjusted [Unadjusted] Baghurst, 1992: -3.3 (1.6) [-8.5 (1.5)] Dietrich, 1993: -1.3 (0.9) [-2.6 (1.5)] Ernhart, 1985: -1.1 (0.9) [-12.1 (1.5)] Cooney, 1991: 0.39 (2.0) Bellinger, 1992: -5.8 (2.1) [-7.1 (2.5)] <u>Cross-Sectional, Blood</u>: Adjusted [Unadjusted] Hatzakis, 1987: -2.7 (0.7) [-3.8 (0.8)] Fulton, 1987: -2.6 (1.0) [-3.8 (1.1)] <u>Cross-Sectional, Tooth</u>: Adjusted [Unadjusted] Smith, 1983: -0.65 (0.54) [-1.84 (0.6)] **<u>Meta-analysis:</u>** Mean (SE) change in IQ for a doubling of body burden of Pb: Prospective @ birth (n=1166): 0.18 (0.62) Prospective @ 2 yrs (n=1197): -1.85 (0.51) Prospective, mean (n=1260): -0.88 (0.58) Cross-sect. Blood (n=3499): -2.53 (0.41) *Cross-sect. Blood (n=3499): -1.74 (0.43) Cross-sect. Tooth (n=2095): -0.95 (0.25) *Wang, 1989 removed: *P* test for heterogeneity was significant when included. Overall conclusion was that a doubling of blood Pb levels from 10 to 20 µg/dL, or tooth Pb from 5 to 10 µg/g was associated with an avg estimated deficit in IQ of ~1-2 points. Authors caution interpretation of these results and Pb literature in general, citing questions about representativeness of the samples, residual confounding, selection bias, and reverse causality.	Blood and tooth Pb were associated with decreases in children's IQ in a meta-analysis, with prospective studies showing an association with age 2 Pb, but not Pb at birth and tooth Pb showing smaller, but consistent, reductions in IQ as well.
Cross-sectional Prpic-Majic (2000) Zagreb, Croatia	275 3rd and 4th grade students from 3 elementary	Calc. mean age: 9.84 years	Blood Pb at time of testing: 7.08 (1.788)	General cognitive development: Wechsler Intelligence	Multiple stepwise regression	Pb was not independently associated with any cognitive test, but if forced into the models: adjβ (95% CI) VIQ: -0.16 (-0.089, 0.057)	Blood and erythrocyte Pb were not

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	schools in urban areas with different traffic conditions in Zagreb, Croatia; Year not stated Male=52%		*Also measured Pb in erythrocytes, ALAD, EP, hemoglobin, and hematocrit*	Scale for children—Revised (WISC-R) including verbal, (VIQ), nonverbal (NIQ), and general intelligence quotient (IQ); Visual motor integration: Bender Gestalt Test Error Score; Attention and complex psychomotor reactions: Complex Reaction-meter Drenovac	Adjusted for age, parental education, and gender	NIQ: -0.031 (-0.121, 0.060) IQ: -0.025 (-0.099, 0.050) *Erythrocyte Pb was also not associated*	associated with intelligence quotients, visual motor integration, or attention and complex psychomotor reactions.
Cross-sectional (Rabinowitz *et al.* 1992) Taiwan	493 children in grades 1-3 of seven primary schools in Taiwan Year not stated % male not stated	mean not stated grades 1-3	Tooth (dentin) Pb 4.6 (3.5) µg/g	Teachers filled out the Boston Teachers Questionnaire (BTQ) to assess academic performance and behavior.	Logistic regression analysis	Incisor Pb levels (>5.6 ppm (Q4) vs. <2.9 ppm (Q1) with teacher reported academic performance and behavior. Girls: Behavior: X^2=4.9; p-value=0.20 Hyperactive: X^2=2.8; p=0.40 Reading: X^2=2.6; p=0.50 Math: X^2=1.8; p=0.60 Directions: X^2=0.50; p-value=0.90 Daydreaming: X^2=0.60; p-value=0.90 Tasks: X^2= 1.1; p-value=0.80 Boys: Behavior: X^2=5.2; p-value=0.16 **Hyperactive: X^2=6.2; p=0.10; X^2 for trend<0.01** Reading: X^2=5.7; p=0.13 Math: X^2=2.4; p=0.50 Directions: X^2=2.7; p-value=0.40 Daydreaming: X^2=0.80; p-value=0.90 **Tasks: X^2= 13.5; p-value=0.004; X^2 for trend<0.005**	Tooth Pb was significantly associated with learning problems (BTQ hyperactivity and tasks) in school aged boys.
Prospective Rajan (2007) Boston, MA, USA *Population may overlap with Payton (1998) and others*	744 participants from the Normative Aging Study (NAS) for whom bone and blood Pb measurements and psychological assessment data was available; Year= 1991 – 2002 (initially enrolled in	67 (7) years	Blood: 6.2 (4.1) µg/dL Tibia: 22.1 (13.8) µg/g Patella: 31.4 (19.6) µg/g Measured beginning in 1991 and	Psychiatric symptoms were assessed by the Brief Symptom Inventory, a self-administered 53-item questionnaire that assesses nine primary symptom dimensions in the last 30 days: anxiety,	Repeated-measures logistic regression models. Age at bone scan, alcohol consumption, education, time between Brief Symptom Inventory assessments, and cumulative smoking	adjOR (95% CI) for an interquartile increment in tibia Pb (14 µg/g) and psychiatric symptoms: Phobic anxiety = 1.13 (0.90, 1.41) **Somatization = 1.21 (1.01, 1.46)** Global severity index = 1.15 (0.96, 1.38) adjOR (95% CI) corresponding to an interquartile increment in patella Pb (20 µg/g): Phobic anxiety = 1.24 (0.99, 1.55) Somatization = 1.09 (0.90, 1.32) **Global severity index = 1.23 (1.02, 1.47)**	Cumulative bone Pb burden was associated with the increased risk of psychiatric symptoms, and significantly associated with somatization (tibia) and

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	1963) Male=100%		subsequently at 3-year intervals in a 6-year period	depression, hostility, interpersonal sensitivity, obsessive-compulsive, paranoid ideation, phobic anxiety, psychoticism, somatization			global severity index (patella)
Cross-sectional Rajan (2008) Boston, MA, USA *Population may overlap with Payton (1998) and others*	982 men from the Normative Aging Study, ; Year=1993-2001 (initially enrolled in 1963) Male=100%	≥49 years 49-61: n=151, 15.4% 62-71: n=474, 48.3% ≥72: n=357, 36.3% *ALAD 1-1:* 49-61 (n=133) 62-71 (n=398) ≥72 (n=287) *ALAD 1-2 & 2-2:* 49-61 (n=18) 62-71 (n=76) ≥72 (n=70)	Calc. means: Blood: 5.3µg/dL Tibia: 21.8µg/g Patella: 29.1µg/g *ALAD 1-1 (n=818)*: Blood: 5.4 (2.9) Tibia: 21.9 (13.8) Patella: 29.3 (19.1) *ALAD-2* carriers (1-2 and 2-2 genotypes, n=164): Blood: 4.8 (2.7) Tibia: 21.2 (11.6) Patella: 27.9 (17.3)	Cognitive test battery included: Consortium to Establish a Registry for Alzheimer's Disease (CERAD; visuospatial, executive function, language, and immediate and delayed verbal memory), the Neurobehavioral Evaluation System (NES; visuospatial, perceptual speed, and visual memory), and the Wechsler Adult Intelligence Scale (WAIS; working memory and general intelligence). All cognitive tests converted to z-scores with a positive score indicating better test performance. *ALAD exon 4 SNP (rs1800435) also genotyped*	Multiple linear regression models (with a smoothing parameter for Pb biomarker, if significantly different from a linear model a likelihood ratio test) Adjusted for main effect of Pb biomarker, *ALAD* genotype age at cognition test, education, alcohol consumption, cumulative smoking, and English as a first language	Adjusted difference in Test z Score Per IQR higher Pb concentration: ALAD 1-2/2-2 vs. ALAD 1–1: Pb*ALAD Parameter Estimate (95% CI) <u>Visuospatial</u> Constructional praxis Blood (n=959): -0.05 (-0.23, 0.13) **Tibia (n=728): -0.25 (-0.49, -0.02), p<0.05** Patella (n=728): 0.02 (-0.19, 0.23) Pattern Memory Blood (n=490): 0.19 (-0.05, 0.42) Tibia (n=397): 0.12 (-0.20, 0.44) Patella (n=395): 0.12 (-0.16, 0.39) Pattern Comparison Blood (n=907): -0.01 (-0.20, 0.18) Tibia (n=705): -0.04 (-0.28, 0.20) Patella (n=705): -0.09 (-0.31, 0.13) <u>Executive function/language/general intelligence</u> Verbal fluency Blood (n=916): -0.03 (-022, 0.16) Tibia (n=709): -0.11 (-0.34, 0.13) Patella (n=709): -0.025 (-0.24, 0.19) Boston naming test Blood (n=500): 0.04 (-0.20, 0.29) Tibia (n=403): -0.16 (-0.50, 0.18) Patella (n=401): -0.15 (-0.44, 0.13) Vocabulary Blood (n=501): -0.21 (-0.43, 0.01), p<0.1 Tibia (n=401): -0.27 (-0.60, 0.05) Patella (n=399): -0.15 (-0.42, 0.12) <u>Verbal memory/working memory</u> Word list memory Blood (n=913): 0.003 (-0.18, 0.19) Tibia (n=708): 0.08 (-0.15, 0.31) Patella (n=708): 0.14 (-0.07, 0.34) Word list delayed recall Blood (n=912): -0.05 (-0.23, 0.13) Tibia (n=707): 0.13 (-0.10, 0.36)	There was no clear pattern of *ALAD* modifying the relationship of Pb to cognition, the cognitive test with a significant *ALAD*-bone interaction were also significantly associated with cumulative Pb burden in a previous report on these same subjects (see Weisskopf et al. (2007b)).

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Patella (n=707): 0.09 (-0.12, 0.30) Digit span backward (total number) Blood (n=863): -0.17 (-0.36, 0.03) Tibia (n=678): -0.12 (-0.36, 0.12) Patella (n=677): -0.005 (-0.22, 0.22) Digit span backward (longest span) Blood (n=864): -0.14 (-0.33, 0.06) Tibia (n=679): -0.06 (-0.30, 0.18) Patella (n=678): 0.02 (-0.20, 0.24) Perceptual speed Continuous performance Blood (n=486): -0.18 (-0.42, 0.06) Tibia (n=392): -0.25 (-0.59, 0.08) Patella (n=390): -0.16 (-0.44, 0.12) Pattern memory Blood (n=490): -0.04 (-0.28, 0.19) Tibia (n=397): -0.08 (-0.41, 0.26) Patella (n=395): 0.06 (-0.22, 0.35) Pattern comparison Blood (n=907): 0.02 (-0.16, 0.20) Tibia (n=705): 0.04 (-0.19, 0.27) Patella (n=705): 0.21 (0.001, 0.41), p<0.1	
Cross-sectional Rhodes, (2003) Boston, MA, USA *Population may overlap with Payton (1998) and others*	526 men in the Normative Aging Study; Year= 1991-1995; (initially enrolled in 1963) Male = 100%	67.1 (7.20) years	Blood: 6.3 (4.16) µg/dL Tibia: 21.9 (13.5) µg/g Patella: 32.2 (19.8) µg/g Bone generally measured within 1 month of blood and BSI (excluded if >3 months)	Mood symptoms evaluated with Brief Symptom Inventory (BSI) included in the Health and Social Behavior Survey at the time of blood collection Measures include: anxiety ≥0.5 (n=77), depression ≥0.5 (n=85), phobic anxiety ≥0.2 (n=40), general severity index > 0.44 (GSI, n=71), positive symptom total >18 (PST, n=83), and combined BSI measure (≥0.5 anxiety, ≥0.5 depression, and ≥0.2	*T* tests were used to compare Pb levels with BSI measures Logistic regression models for each BSI outcome (â) Adjusting for age, age^2, alcohol intake, employment status, and education status Odds ratios estimated from β coefficients for an increase from the midpoints of the lowest to the highest quintile	Anxiety: mean ≥0.5, mean <0.5, p; â (SE), *P* Blood: 6.5, 6.2, NS; 0.0241 (0.0293), 0.41 Tibia:22.4, 21.8, NS; 0.0046 (0.0097), 0.64 Patella:35.6, 31.5, p<0.1; 0.0112 (0.0062), 0.07 Depression: mean ≥0.5, mean <0.5, p; â (SE), *P* Blood: 6.6, 6.2, NS; 0.0275 (0.0285), 0.33 Tibia: 23.4, 21.6, NS; 0.0067 (0.0090), 0.45 **Patella: 36.5, 31.3, p<0.05**; 0.0109 (0.0059), 0.07 Phobic Anxiety: mean ≥0.2, mean <0.2, p; â (SE), *P* Blood: 7.3, 6.2, NS; 0.0541 (0.0349), 0.12 **Tibia: 26.3, 21.5, p<0.05;** 0.0151 (0.0107), 0.16 **Patella: 40.3, 31.5, p<0.05; 0.0144 (0.0072), 0.05** GSI: mean >0.44, mean 0.44, p; â (SE), *P* Blood: 6.8, 6.2, NS; 0.0436 (0.0291), 0.13 Tibia: 23.5, 21.6, NS; 0.0036 (0.0098), 0.72 Patella: 36.3, 31.5, p<0.1; 0.0082 (0.0064), 0.20 PST: mean >18, mean 18, p; â (SE), *P* Blood: 6.4, 6.3, NS; 0.0161 (0.0293), 0.58 Tibia: 23.4, 21.6, NS; 0.0058 (0.0092), 0.53 Patella: 35.3, 31.5, p<0.15; 0.0071 (0.0061), 0.25 Combined BSI: mean >, mean <, p; â (SE), *P* **Blood: 8.8, 6.2, p<0.05; 0.1201 (0.0423), 0.005** **Tibia: 31.8, 21.5, p<0.05; 0.0271 (0.0127), 0.03**	Blood and tibia, and patella Pb were significantly associated with a combined mood measure (including elevated anxiety, depression, and phobic anxiety); patella Pb was significantly associated with depression; and tibia and patella Pb were significantly associated with phobic anxiety.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				phobic anxiety, n=20)		**Patella: 51.8, 31.4, p<0.05; 0.0286 (0.0091), 0.002** Odds Ratio and 95% CI for a low-high quintile increase: **Phobic Anxiety, Patella (45µg/g): 1.91 (1.01-3.61)** **Combined BSI, Blood (8.9µg/dL): 2.91 (1.39-6.09)** **Combined BSI, Tibia (27µg/g): 2.08 (1.06-4.07)** **Combined BSI, Patella (45µg/g): 3.62 (1.62-8.08)**	
Prospective Ris (2004) Cincinnati, OH, USA *Population may overlap with Dietrich (1987) and others*	195 children from the Cincinnati Lead Study (CLS); Year=1997-1999 Male=54%	15.6 (0.8) Range: 15-17	Maternal prenatal = 8.9 (3.9) measured in 1st or early 2nd trimester Average Childhood (first five years) mean not reported 78 months (6.5 years) mean not reported	Neuropsychological measures: executive (Wisconsin Card Sorting Test-WCST; Rey-Osterrieth Complex Figure-ROCF), attention (Continuous Performance Test-CPT), memory (California Verbal Learning Test-CVLT-C), achievement (Wide Range Achievement Test-3rd Ed-SRAT-3); verbal (vocabular subtest), visuoconstruction (Block Design Subtest-BD), fine-motor (Grooved Pegboard Test-Gpegs; Finger Tapping Test-Tapping)	Stepwise multiple regression Adjustments differ by endpoint including maternal IQ, SES, and average HOME score, sex, and adolescent marijuana consumption,	Adjusted relationships between neuropsychological factors and blood Pb variables: Memory Prenatal Pb: β (SE)= -0.002 (0.02), p=0.89 Avg Childhood Pb: β (SE)= 0.003 (0.015), p=0.79 78 months Pb: β (SE)= 0.013 (0.17), p=0.43 Learning/IQ Prenatal Pb: β (SE)= -0.075 (0.54), p=0.17 Avg Childhood Pb: β (SE)= -0.034 (0.029), p=0.25 78 months Pb: β (SE)= -0.081 (0.043), p=0.06 Attention **Prenatal Pb: β (SE)= -0.156 (0.06), p=0.001** **Avg Childhood Pb: β (SE)= -0.133(0.04), p= 0.005** **78 months Pb: β (SE)= -0.119 (0.051), p= 0.02** **Authors state a significant blood Pb x sex interaction (p<0.003-0.0004) with significant associations for males only**. Visuoconstruction **Prenatal Pb: β (SE)= -0.157 (0.061), p= 0.011** Avg Childhood Pb: β (SE)=-0.028 (0.041), p=0.50 78 months Pb: β (SE)=0.014 (0.052), p=0.79 **Authors state a significant blood Pb x sex interaction (p<0.27-0.05) with significant associations for males only**. Fine-motor Prenatal Pb: β (SE)= -0.017 (0.02), p= 0.42 Avg Childhood Pb: β (SE)= -0.016 (0.013), p=0.21 **78 months Pb: β (SE)= -0.046 (0.016), p= 0.004**	Maternal prenatal blood Pb was significantly associated with decreased attention and visuo-construction scores; blood Pb at 78 months was associated with decreased attention and fine-motor scores; and average childhood blood Pb was significantly associated with decreased attention scores – all neuropsychological measures at age 15-17.
Prospective Rothenberg (1989) Mexico City, Mexico *Population may overlap with Rothenberg (1994)*	42 infants in the Mexico City Prospective Lead Study of women recruited at the National Institute of Perinatology and the General Hospital in Mexico	48 hours; 15 and 30 days	Maternal at 36 weeks: 15.0(6.4) Maternal at delivery: 15.5(5.7) Cord: 13.1(6.0)	Brazelton Neonatal Behavioral Assessment Scale (NBAS) administered in the hospital and at 15 and 30 days after birth; 7 NBAS cluster scales calculated from each NBAS	Bivariate correlations; forward multiple regression analyses; multiple regression analyses	Effect of Pb on NBAS scales in multiple regression models: Difference in maternal Pb (36 weeks and delivery) **Regulation of State (15 days):** **Partial r^2=0.068; p=0.049; coefficient=0.101** Regulation of State (30 days): Partial r^2=0.061 ; p= 0.055; coefficient = 0.091 Autonomic Regulation (30 days): Partial r^2= 0.048 ; p=0.073; coefficient=-0.022	Change in maternal blood Pb level between 36 weeks and delivery predicted NBAS regulation of state at 15

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
and others	City on or before their 36th week of pregnancy. Year not stated % male not stated			protocol sheet		 <u>Maternal at delivery and cord</u> Regulation of State (30 days): Partial r^2= 0.071 ; p=0.042; coefficient = -0.136 <u>Difference between Maternal at 36 weeks and cord Pb</u> **Autonomic Regulation (30 days):** **Partial r^2= 0.047; p=0.047; coefficient= -0.024**	days. Difference in maternal Pb at 36 weeks and cord Pb predicted NBAS autonomic regulation at 30 days
Prospective Rothenberg (1994) Mexico City, Mexico *Population may overlap with Rothenberg (1989) and others*	30 babies, the last born in the Mexico City Prospective Lead Study of women recruited from the National Institute of Perinatology and the General Hospital in Mexico City at a gestational age range of 36.5-41.9 weeks and no major congenital. anomalies; Year not stated % male not stated	Median: 9 days (range 2 - 39 days); 3 months	mean not reported Maternal blood Pb measured 12, 20, 28, 36 weeks, delivery; cord Pb measured at birth	Brainstem auditory evoked responses (BAER)	Pearson correlation	Pearson correlation for maternal blood Pb (at 12, 20, 28, or 36 weeks of pregnancy; delivery and cord blood Pb): <u>Latency of Wave I</u> **20 wks r=-0.42; p=0.03** <u>Latency of Peak II</u> **20 wks r=-0.39; p=0.04** **28 wks r=-0.51; p=0.005** **36 wks r=-0.52; p=0.007** **maternal at delivery r=-0.44; p=0.03** **cord Pb r=-0.44; p=0.02** <u>I-V interpeak interval</u> **12 wks r=0.46; p=0.03** <u>III-V interpeak interval</u> **12 wks r=0.51; p=0.02** **20 wks r=0.57; p=0.002** **28 wks r=0.45; p=0.01** **36 wks r=0.51; p=0.009** Other correlations were not statistically significant	Maternal blood Pb during pregnancy was significantly associated with decreased latency of waves I and peak II and increased interpeak I-V and III-V interval. Cord blood PB and maternal blood Pb at delivery was significantly associated with latency of peak II.
Prospective Rothenberg (2000) Mexico City, Mexico *Population may overlap with Rothenberg (1989) and others*	100 in the Mexico City Prospective Lead Study of women recruited at the National Institute of Perinatology and the General Hospital in Mexico City on or before their 36th week of pregnancy. Year not stated % male not stated	5.5 years Range: 5-6 years	Geometric means Maternal (20-wks) = 8.1(+8.1/-4.0) Infant Cord=8.7(+8.4/-4.3) 12 mo. not reported 18 mo.=10.8(+9.4/-5.2) 48 mo. not reported 60 mo.=8.0 (+6.2/-3.7) Abstract presents different mean for	Brainstem auditory evoked response (BAER), head circumference	Linear multiple regression; orthogonal polynomial multiple regression, t-test, ANOVA Head circumference, age at time of testing, and sex	Effect of 20-week maternal blood Pb on BAER interval (milliseconds) <u>Interval I-V</u> Linear multiple regression ln (Pb) β (95% CI): β= -0.044 (-0.097, 0.009); p=0.106 **Orthogonal polynomial multiple regression** **Linear component ln(Pb) β (95% CI):** **β= -0.045 (-0.082, -0.008), p=0.018** **Quadratic component ln(Pb) β (95% CI):** **β= 0.050 (0.016, 0.084), p=0.004** <u>Interval III-V</u> **Linear multiple regression ln(Pb) β (95% CI):** **β= -0.051 (-0.100, -0.002), p=0.044** **Orthogonal polynomial multiple regression**	Maternal blood Pb (20 week) and postnatal blood Pb (12 and 48 month) was significantly associated with changes in the BAER I-V and III-V inter-peak intervals.

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			maternal Pb (7.7; range 1–30.5)			**Linear component ln(Pb) β (95% CI):** **β= -0.048 (-0.083, -0.014), p=0.007** **Quadratic component ln(Pb) β (95% CI):** **β= 0.044 (0.013, 0.075), p=0.007** Effect of 12-mo. infant blood Pb on BAER interval (ms) Interval I-V Linear multiple regression ln (Pb) β (95% CI): **β= -0.063 (-0.123, -0.003); p=0.044** Interval III-V Linear multiple regression ln(Pb) β (95% CI): β= -0.031 (-0.089, 0.026), p=0.278 Effect of 48-mo. infant blood Pb on BAER interval (ms) Interval I-V Linear multiple regression ln (Pb) β (95% CI): **β= -0.084 (-0.161, -0.007); p=0.033** Interval III-V Linear multiple regression ln(Pb) β (95% CI): **β= -0.076 (-0.149, -0.003), p=0.040** Authors also report association between maternal and infant blood Pb level and head circumference at 72 mo.	
Prospective Rothenberg (2002) Mexico City, Mexico *Population may overlap with Rothenberg (1989) and others*	45 participants in the Mexico City Prospective Lead Study of women recruited at the National Institute of Perinatology and the General Hospital in Mexico City on or before their 36th week of pregnancy with normal visual acuity. Year not stated Male= 47%	109 (11.3) months =9.08 years Range: 84-124 months (age 7-10)	Maternal (12 weeks): tertile med. (range) T1 (ref) = 4.0 (2-5.5) T2 (low) = 8.5 (6-10) T3 (mod) = 14.0 (10.5-32.5) Child at testing: tertile median (range) T1 (ref) = 4.0 (2-4.5) T2 (low) = 6.0 (5-6.5) T3 (mod) = 7.5 (7-16) Pb measured at 12 weeks gestation and then every 8 weeks, maternal and cord blood at birth, and child every 6 months until ERG testing.	Children were assessed for retinal function by electroretinographic (ERG) testing: full-field scotopic flash ERGs were recorded over a 4-log-unit range (-1.37 to +1.85 log scotopic troland/second [scot td/sec]). Scotopic voltage (V)-log intensity (I) and implicit time (IT)-log I functions were generated. Serum Fe, Zn, and retinol also measured.	Repeated measures ANOVA; simple ANOVA with the Tukey honest significant difference method; Huynh-Feldt corrected degrees of freedom for F-tests. Pearson correlation coefficients	Repeated-measures ANOVA showed that only maternal 12 week showed a dose-response relationship with ERG measures. Increase in ERG with increasing 12 week maternal Pb **a-wave amplitude (+12 ms): $F_{2,36}$=4.104, p= 0.025** **a-wave amplitude (peak): $F_{2,36}$=5.75, p=0.007** **b-wave amplitude: $F_{2,36}$=5.75, p= 0.007** Pearson correlation coefficients of blood Pb and ERG testing: Maternal 12 weeks; Child @ testing (Coeff., *P*) a-Wave peak amplitude (scot td/sec) -0.36: M 0.103, *P*=0.532; C -0.042, *P*=0.783 **+0.37: M 0.459, *P*=0.003;** C 0.050, *P*=0.743 **+0.88: M 0.460, *P*=0.003**; C 0.056, *P*=0.713 **+1.35: M 0.364, *P*=0.023;** C 0.107, *P*=0.484 **+1.85: M 0.341, *P*=0.033;** C 0.210, *P*=0.167 b-Wave amplitude (scot td/sec) **-0.36: M 0.421, *P*=0.008;** C 0.118, *P*=0.440 **+0.37: M 0.439, *P*=0.005;** C 0.107, *P*=0.485 **+0.88: M 0.339, *P*=0.035;** C 0.219, *P*=0.148 +1.35: M 0.249, *P*=0.126; C 0.019, *P*=0.901 +1.85: M 0.281, *P*=0.083; C 0.043, *P*=0.781	Maternal blood Pb levels during the first trimester were significantly associated with increases in leading-edge a-wave amplitude, peak a-wave amplitude, and b-wave amplitude in 7 to 10-year old children
Cross-sectional Roy (2009) Chennai, India	756 elementary school children in Chennai; Years=	mean not reported Range:3-7	11.4(5.3)	Neurobehavior assessment (Conners' ADHD/	Multivariate generalized estimating equations (GEE) analysis	Multivariate GEE analysis of log blood Pb and teacher reported behavior raw scores: β (95% CI) **Anxiety β=0.27(0.05-0.51); *p* = 0.02**	Concurrent blood Pb levels were

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	2005-2006 Male=53.4%			Diagnostic and Statistical Manual for Mental Disorders, 4th Ed. (DSM-IV) Scales (CADS-T), Conners' Teacher Rating Scales-39 and Behavior Rating Inventory of Executive Function	Child's age (months), sex, hemoglobin level, family average monthly income, maternal and paternal education, number of other children, clustering at the class and school level	**Social problems β=0.20(0.02-0.038);*p* = 0.03** **ADHD index β= 0.17(0.00-0.36); *p* = 0.05** **DSM-IV inattentive β=0.24(0.05-0.43); *p* = 0.01** DSM-IV hyperactive β=0.13(-0.04-0.30); *p* = 0.13 **Global exec. func. β=0.42(0.18-0.65); *p* < 0.001** The authors reported similar value for GEE analysis by Z-score and stated there was no difference by sex	significantly associated with behavior scores indicating more anxiety, social problems, ADHD, and decreased executive function in 3-7 year old children.
Prospective Schnaas, (2000) Mexico City, Mexico *Population may overlap with Rothenberg (1989) and others*	112 children in the Mexico City Prospective Lead Study of women recruited at the National Institute of Perinatology and the General Hospital in Mexico City on or before their 36th week of pregnancy Year not stated Male = 47.3%	6-54 months	Geom. mean (range) 6-18 months: 10.1 (3.5-37.0) 24-36 months: 9.7 (3.0-42.7) 42-54 months: 8.4 (2.5-44.8) Blood Pb measured every 6 months from 6 to 54 months	Intellectual status indexed by General Cognitive Index (GCI) from McCarthy Scales of Children's Abilities (MSCA).	Repeated measures ANCOVA 5-min Apgar, birth weight, birth order, sex, socioeconomic level, maternal IQ, and maximum maternal education al level	<u>Test for interaction between blood Pb and age at which the GCI was determined (within-subject effect):</u> **6-18 month Pb: p=0.076 (linear effect p = 0.047)** **24-36 month Pb: p=0.044 quadratic effect (p = 0.019)** 42-56 month Pb: p=0.632 <u>Estimated regression coefficients and SEs of the effect of blood Pb on GCI</u> (Figure, summarized below): 6-18 month blood Pb did not have a significant effect of GCI at any age (p>0.1). **Increasing blood Pb at 24-36 months was significantly associated with a decreased GCI at 48 (p = 0.021) and 54 months (p=0.073).** **Increasing blood Pb at 42-54 months was significantly associated with a decreased GCI at 54 (p = 0.040) and 60 months (p=0.060).**	Postnatal blood Pb was significantly associated with lower GCI scores with a maximum effect approximately 1 to 3 years after Pb measurement.
Prospective Schnaas (2006) Mexico City, Mexico *Population may overlap with Rothenberg (1989) and others*	150 children the Mexico City Prospective Lead Study of women recruited at the National Institute of Perinatology and the General Hospital in Mexico City on or before their 36th week of pregnancy Year=1987-2002 Male=52.7%	mean not reported 6 - 10 years	Geometric means (5th-95th) Maternal Pb: 12-20 weeks = 8.2 (3.0, 20.7) 28-36 wks = 7.8 (2.5, 24.6) Cord Pb= not reported	Full-scale IQ (FSIQ) as assessed using the Wechsler Intelligence Scale for Children–Revised (WISC-R; Spanish version) under standardized conditions	Multivariate regression; linear mixed model Maternal IQ, SES, sex, birth weight, and an indicator variable of first FSIQ application at 6, 7, or 8 years	<u>Multivariate regression analysis of ln(blood Pb) and IQ scores</u>: β (95% CI): Maternal Pb: 12-20 weeks: -1.45 (-4.75, 2.00); p = 0.42 **28-36 weeks: -4.00 (-6.37, -1.65); p = 0.001** At delivery: -1.29 (-4.41, 1.83); p = 0.41 Cord Pb: -0.95 (-3.65, 1.75); p = 0.49	Maternal blood Pb at 28-36 weeks was significantly associated with reduced IQ at 6-10 years.
Cross sectional (Schwartz and Otto 1987)	4,519 subjects from NHANES II Year=1976-1980	mean not reported Range 4-19 yrs	mean not reported *limits utility	Elevated hearing thresholds above the standard reference	Multiple regression, logistic regression	<u>Hearing threshold (in decibels) for 4 frequencies for children (age 6-19), blood Pb estimate:</u> Coeff; p-value Left Ear:	Concurrent blood Pb was significantly

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
USA	% male not stated			level (500, 1000, 2000, and 4000 Hz) and developmental milestones	Race, sex, current cold, ringing in ears, cold in last 2 weeks, ear discharge, ringing in ears, earache, previous running ear, other ear conditions, diagnosed hearing impairment, income, chronic ear discharge, degree of urbanization, dietary calcium, head of household education level	**500 Hz: 0.0547; p<0.0001** **1000 Hz:0.0447; p<0.0001** **2000 Hz: 0.0487; p<0.0001** **4000 Hz:0.0517; p<0.0001** Right Ear: **500 Hz: 0.0533; p<0.0001** **1000 Hz:0.0651; p<0.0001** **2000 Hz: 0.0600; p<0.0001** **4000 Hz:0.0567; p<0.0001** Developmental milestones for children (age 6-19), blood Pb estimate: Coeff; p-value **Age (in yr) of first word: 0.0024; *p* = 0.0094** **Age (in mo) when first walked: 0.0070, *p* = 0.0020** **Age (in mo) when first sat up: 0.0061, *p* = 0.0239** **Prob. of being hyperactive (logistic): 0.0116, *p* = 0.0150**	associated with elevated hearing thresholds at 500, 1000, 2000 and 4000 Hz in both ears and delays in developmental milestones, but blood Pb levels are not described and means were above 10µg/dl in other NHANES II studies.
Cross-sectional (Schwartz and Otto 1991) USA	3545 subjects from the Hispanic Health and Nutrition Survey (HHANES) Year=1982-1984; % male not stated	6-19 years	Median: 8	Elevated hearing thresholds above the standard reference level (500, 1000, 2000, and 4000 Hz)	Linear regression Covariates include family income and ethnicity; others considered include current cold, cold during past week, and sex	Hearing threshold (average of both ears, in decibels) for 4 frequencies for children (age 6-19), blood Pb estimate: Coeff; p-value Left Ear: **500 Hz: 0.0466; p=0.0.014** **1000 Hz: 0.0274; p=0.0.029** **2000 Hz: 0.044; p<0.001** **4000 Hz: 0.019; p=0.049** Right Ear: **500 Hz: 0.034; p=0.023** **1000 Hz: 0.039; p=0.007** **2000 Hz: 0.039; p=0.009** 4000 Hz: NS Hearing threshold (average of both ears, in decibels) for 4 frequencies for children (age 6-19), blood Pb estimate: Coeff; p-value **500 Hz: 0.00452; p<0.001** **1000 Hz:0.00457; p<0.001** **2000 Hz: 0.00470; p<0.001** **4000 Hz:0.00368; p<0.017** An increase in blood Pb from 6 to 18µg/dL was associated with an additional 15% of children who had hearing thresholds below the standard at 2000Hz. An increase in blood Pb from 6 to 18µg/dL was associated with a 2-dB loss in hearing at all frequencies	Concurrent blood Pb was associated with increased risk of hearing thresholds above the standard (500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz)

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Meta-analysis Schwartz (1994)	Meta-analysis of 7 studies of blood Pb and full-scale IQ in school age children: 3 longitudinal (Bellinger (1992), Dietrich (1993b), and Baghurst (1992)) and 4 cross-sectional (Hawk (1986), Hatzakis (1987), Fulton (1987), and Yule (1981)).	School aged children (mean ages not reported)	Longitudinal (Blood Pb at age 2-3 years): Bellinger, 1992: 6.5 Dietrich, 1993: 15 Baghurst, 1992: 20 Cross-sectional: Hawk, 1986: 21 Hatzakis, 1987: 23 Fulton, 1987: 12 Yule, 1981: 13 *Silva, 1988: 11 *Silva, 1988 was not included in the primary meta-analysis for analytical reasons.	Full-scale IQ (scales used varied between studies)	Predicted change in IQ as blood PB increased from 10 to 20 µg/dL. Studies were weighted by the inverse of the variances and a random effects model. Adjustments varied by study and all except Yule and Silva included parental IQ and HOME score. Also considered population SES († = disadvantaged)	Estimated decrease in IQ from an increase in blood Pb from 10 to20 µg/dL: point decrease ± SE ‡Bellinger, 1992: 5.8 ± 2.1 †‡Dietrich, 1993: 1.3 ± 0.9 Baghurst, 1992: 3.33 ± 1.46 †Hawk, 1986: 2.55 ± 1.5 Hatzakis, 1987: 2.66 ± 0.7 ‡Fulton, 1987: 2.56 ± 0.91 †‡Yule, 1981: 5.6 ± 3.2 Silva, 1988: 1.51 (SE couldn't be calculated*) **Meta-analysis: 2.56 ± 0.41, P < 0.001** Sensitivity Analyses: Exclude largest effect study (Bellinger): 2.43 ± 0.34 Exclude most sig. Study (Hatzakis): 2.52 ± 0.58 Include Silva (no weighting): 3.16 ± 0.60 Adding 8 studies with 0 effect size: ↓50%, *P* < 0.01 Longitudinal studies only: 2.96 ± 1.25 Cross-sectional studies only: 2.69 ± 0.51 Disadvantaged populations (†): 1.85 ± 0.92 Non-disadvantaged: 2.89 ± 0.50 Studies with mean blood Pb ≤ 15µg/dL (‡): 3.23 ± 0.92 Studies with mean blood Pb > 15µg/dL: 2.32 ± 0.40 Authors suggest that a threshold at 10µg/dL is implausible because effect is larger below 15µg/dL. In the study with the lowest blood Pb level (Bellinger, 1992), was examined alone using nonparametric smoothing, no evidence of a threshold was observed down to a blood Pb level of 1 µg/dL.	Blood Pb was signinficantly associated with lower IQ in school age children in this meta-analysis of 7 studies. The authors conclude that these data provide further evidence of Pb effects on cognition below 10 µg/dL - with no evidence of a threshold.
Cross-sectional Sciarillo (1992) Baltimore, MD, USA	201 African-American children aged 2-5 years recruited from the Baltimore Soil Lead Abatement Demonstration Project and the Kennedy Krieger Institute's Lead Poisoning Referral Center; Year=1989 % male not stated	mean not reported 2 - 5 years,	High (n=78, ≥15µg/dL on 2 visits): Prior: 28.6 (9.3) During: 27.8 (10.4) Low (n=123): Prior: 11.3 (4.3) During: 9.2 (2.9)	Child behavior as reported by the mother on the Achenbach Child Behavior Checklist (CBCL) and as a control measure the Center for Epidemiologic Studies Depression Scale (CES-D).	χ^2 test of difference is T-scores above the clinical 90th percentile, Odds ratio for being in the 98th percentile if exposed to high Pb Multiple linear regression including maternal education, occupation, marital status, ≥ preschool children in the home,	CBCL T-Scores (>90th): Low %/High %, χ^2, *P* value (1df) **Total:16.3%/32.0%, 6.85, *P* < 0.01** Internalizing: 10.6%/19.2%, 2.99, *P* = 0.08 **Externalizing: 14.6%/25.6%, 3.77, *P* = 0.05** Total CBCL Total Score (>98th): Low=17.9%, High=30.8%, OR=2.0 (95% CI 1.0-4.0) Multiple linear regression on CBC Total Score **Blood Pb (µg/dL): 0.18 (SE 0.073), *P* = 0.0125**	Blood Pb was significantly associated with worse behavior (on CBCL) in children age 2-5; those with blood Pb over 15µg/dL had significantly higher Externalizing scores as well.

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					CES-D, child's age, sex, and iron deficiency		
Prospective Shen (1998) Shanghai, China	133 mother/infant pairs at the Yangpu Maternal and Child Health Center: 66 in the high Pb group (blood Pb>70th percentile) and 62 in the low Pb group (blood Pb<30th percentile); Year=1993 Male=0%, mothers	3, 6, and 12 months	Cord blood Pb: All: 9.2 (8.86, 9.54) High Pb group: 13.4 (2.0) Low Pb group: 5.3 (1.4) (geometric means)	Child development as assessed by the Mental Development Index (MDI) and the Psychomotor Development Index (PDI) of the Bayley Scales of Infant Development	Single-variate analyses and multiple-variate analyses gestational age, parental occupational exposure to Pb, parity, viral infection during pregnancy, passive smoking during pregnancy, premature rupture of the membranes, father's age at birth of child, maternal Hb level at mid-term pregnancy	Comparison of developmental index of high Pb group vs. low Pb group: 3 months: **MDI: p=0.0187** PDI: p=0.0702 6 months: **MDI: p=0.0315** PDI: p=0.2706 12 months: **MDI: p=0.0279** PDI: p=0.5831	Cord blood Pb was significantly associated with MDI, but not PDI, scores at ages 3, 6, and 12 months
Prospective Shih (2006) Baltimore, MD, USA *Population may overlap with Glass (2009) and others*	985 older adults in the Baltimore Memory Study; Year not stated Male=34.1%	59.39 (5.96)	Blood Pb= 3.46 (2.23) Tibia =18.72 (11.24)µg/g	Cognitive assessment by 20 tests grouped into 7 cognitive domains: language (Boston Naming, letter fluency, and category fluency), processing speed (simple reaction time), eye-hand coordination (Purdue pegboard, Stroop C form minus A form, and trail-making test A), verbal memory and learning (Rey auditory verbal learning test), visual memory (Rey complex figure recall and symbol digit), and visuo-construction (Rey complex figure copy).	Multiple linear regression; Age, sex, technician, presence of APOE-ε4 allele	Change in domain score (β) per 1 µg/dL Blood Pb β(SE): Language β= -0.0060 (0.0118) Processing speed β= -0.0109 (0.0109) Eye-hand coordination β= -0.0110 (0.0106) Executive function β= -0.0143 (0.0099) Verbal mem. & learning β= -0.0181 (0.0124) Visual memory β= -0.0137 (0.0121) Visuconstruction β= -0.0191 (0.0138) *Further adjustment for education, wealth, and race/ethnicity did not make any statistically significant Change in domain score (β) per 1 µg/g Tibia Pb β(SE): **Language β= -0.0083 (0.0023), $p \leq 0.01$** **Processing speed β=-0.0042 (0.0021), $0.01 < p \leq 0.05$** **Eye-hand coordination β=-0.0079 (0.0020), $p \leq 0.01$** **Executive function β=-0.0075 (0.0019), $p \leq 0.01$** **Verbal mem. & learning β=-0.0078 (0.0024), $p \leq 0.01$** **Visual memory β=-0.0067 (0.0023), $p \leq 0.01$** **Visuconstruction β=-0.0122 (0.0027), $p \leq 0.01$** *After further adjustment for education, wealth, and race/ethnicity, no p-values remained < 0.05.	Tibia Pb was significantly associated with lower scores on all 7 domains of cognitive function in in older adults; while blood Pb was not significantly associated with any domain.

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Cross-sectional Silva (1988) New Zealand	579 children born in Dunedin's only obstetric hospital who were part of the 11-yr follow-up of the Dunedin Multidisciplinary Health and Development Study. Year not stated % male not stated	11 years	All children: 11.1(4.91) Boys: 11.4(4.57) Girls:10.4(4.6) (at age 11)	Intelligence was assessed using the WISC-R; behavioral problems were assessed by the Parents' and Teachers' Rutter Behavioral Scale; the Parents' and Teachers' Hyperactivity Scale; the Teachers' Inattention Scale	Pearson correlation Socio-economic status, changes of residence, frequent changes of school, solo parenting, separation of child from his or her parents, mother's age at birth of first child, maternal cognitive ability, family relations, marriage guidance, mental health symptoms, mother's age, child's sex, ordinal position in the family	Correlations between log blood Pb levels and the cognitive and behavior measures scores at age 11: Verbal IQ: r=-0.06; NS Performance IQ: r=-0.03; NS Full Scale IQ: r=-0.05; NS **Reading: r=-0.09; p<0.05** **Parents' Rutter Behavior Scale: r=0.14; p<0.001** **Teachers' Rutter Behavior Scale: r=0.14; p<0.001** **Parents' Inattention Scale: r=0.11; p<0.01** **Parents' Hyperactivity Scale: r=0.14; p<0.001** **Parents' Inattention Scale: r=0.19; p<0.001** **Parents' Hyperactivity Scale: r=0.14; p<0.001** *N.B. it is not clear from the data table in the article why "parents" rating for Inattention and Hyperactivity are listed twice, or if one should be "teachers" rating*	Concurrent blood Pb was significantly correlated with behavioral problems, but not with IQ, at age 11.
Cross-sectional Solon (2008) Visayas, Philippines	877 children aged 6 to 59 months from the Quality Improvement Demonstration Study in the central Philippines. Year=2003-2004 % male not stated	mean not stated Range = 6 to 59 months	7.1 µg/dL Concurrent blood Pb levels measured upon recruitment into study	Cognitive development in children aged 6 to 36 months measured using the Bayley Scales of Infant Development (BSID-II), consisting of a Mental Developmental Index (MDI) and a Psychomotor Development Index (PDI); Children aged 3 to 5 years were tested using the Wechsler Preschool and Primary Scales of Intelligence (WPPSI), consisting of Verbal IQ and Performance IQ	2-stage least squares regression models Roof material, water source, sex, history of breast feeding, prematurity, mother's IQ or education, maternal tobacco use during pregnancy, yearly household income.	Children aged 6 to 36 months: 1 µg/dL increase in blood Pb and change in BSID-II scores: **-3.32 (-5.02, -1.6) points; p<0.01** Children aged 3 to 5 years: 1 µg/dL increase in blood Pb and change in WPPS-III VIQ scores: **-2.47 (-4.58, -0.35) points; p=0.02**	Concurrent blood Pb was significantly associated with lower cognitive development scores in children.
Prospective Stiles (1993) Boston, MA, USA *Population may overlap with*	148 children from the Boston Lead Study born at the Brigham and Women's Hospital were re-evaluated	10 years	Low: <5µg/dL Medium: 5-9.9µg/dL High: ≥10µg/dL Measured at birth (cord), 6, 12, 18, 24,	Neuropsychological tests used were WISC-R, K-TEA, the California Verbal Learning Test for children (CVLT-C),	Multiple regression HOME score, child stress, maternal IQ, socioeconomic status, sex, and birth order	Regression coefficients (SE) associated with blood Pb at 24 months: <u>WISC-R Scores</u> **Full Scale IQ: -0.58 (0.21); p=0.007** **Verbal IQ: -0.63 (0.22); p=0.004** Performance IQ: -0.39 (0.23); p=0.091	Blood Pb at 24 months was significantly associated worse cognitive function,

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Bellinger (1984) and others	at 10 yrs of age. Year=born between 1979-1981 % male not stated		57 months and 10 years.	Wisconsin Card Sorting Test (WCST), Developmental Test of Visual-Motor Integration (VMI), Test of Visual-Motor Integration, Rey-Osterieth Complex Figure (ROCF), Story Recall, Finger Tapping, and Grooved Pegboard.		Information: -0.07 90.05); p=0.13 **Similarities: -0.13 (0.05); p=0.011** **Arithmetic: -0.12 (0.04); p=0.010** Vocabulary: -0.08 (0.04); 0.090 **Comprehension: -0.10 (0.04); p=0.018** Digit Span: -0.09 (0.05); p=0.056 **Blood design: -0.11 (0.06); p=0.043** Coding: -0.05 (0.05); p=0.35 **CVLT-C: 0.03 (0.01); p=0.013** Story Recall Delayed recall score: -0.14 (0.08); p=0.089 VMI: NS **ROCF: -0.12 (0.06); p=0.047** **Grooved pegboard: 0.04 (0.02); p=0.025**	including full scale and verbal IQ, on several subscales of WISC-R at age 10.
Prospective Surkan (2007) ME and MA, USA	New England Children's Amalgam Trial (NECAT): 511 English-speaking children with no prior or existing amalgam restorations and had two or more posterior teeth with dental caries Year= 2003 Male=46%	8.0 years (range = 6 to 11.5)	mean not reported Blood Pb measured at baseline	Primary tests: The Full-Scale IQ on the Wechsler Intelligence Scale for Children (WISC-III); Secondary outcomes: Wechsler Individual Achievement Test (WIAT); battery of additional neuropsychological tests: the Wide Range Assessment of Visual Motor Ability (WRAVMA), the Wide Range Assessment of Memory and Learning (WRAML), the Stroop Color-Word Interference Test, the Wisconsin Card Sorting Test (WCST), the Trail-making Test; Caregiver IQ measured using Kaufman-Brief Intelligence Test (K-BIT); Life Stress score	Multivariate analysis of covariance Adult IQ, age, socioeconomic status, race, and birth weight	Dose-response model of blood Pb and WISC-III: β (SE) Full-scale IQ 1-2 µg/dL: reference 3-4 µg/dL: -0.12 (1.62); p=0.941 **5-10 µg/dL: -6.04 (2.39); p=0.012** Verbal IQ 1-2 µg/dL: reference 3-4 µg/dL: -0.86 (1.66); p=0.605 **5-10 µg/dL: -5.37 (2.63); p=0.016** Performance IQ 1-2 µg/dL: reference 3-4 µg/dL: 0.05 (1.78); p=0.978 **5-10 µg/dL: -5.37 (2.63); p=0.042** Dose response model of blood Pb and WIAT: β (SE) Reading 1-2 µg/dL: reference 3-4 µg/dL: -1.01 (1.74); p=0.564 **5-10 µg/dL: -8.74 (2.57); p=0.001** Math 1-2 µg/dL: reference 3-4 µg/dL: 1.54 (1.61); p=0.340 **5-10 µg/dL: -7.92 (2.38); p=0.001** Authors also report significant effects at blood Pb of 5-10µg/dL on: WIAT scales in basic reading, reading comprehension, mathematics reasoning, numeric operations, listening comprehension WRAVMA – composite and subtest matching (not drawing or pegboard)	Blood Pb levels of 5-10 µg/dL were significantly associated with measures of compromised cognition and decreased attention and working memory, when compared to levels between 1 and 2 µg/dL.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				measured with the Parenting Stress Index		WRAML – indices of general memory, visual memory, verbal memory (not learning index); scales finger windows and sentence memory (not other scales) WCST – preservation errors and number of categories achieved (not trials to the first category)	
Prospective Surkan (2008) Mexico City, Mexico *Population may overlap with Tellez-Rojo (2006), Gomaa (2002) and others*	379 mother-child pairs from 3 cohorts of the Harvard-Mexico Project on Fetal Pb Exposure, Risks and Intervention Strategies (FLERIS). Year=1996-2001 (n=247) and 2004-2005 (n=132) Male=57%	Assessed 12-36 months Mean maternal age at delivery: 26.0 (5.5)	At 24 months (n=319): 6.4 (4.3) Range 0.8-25.8	Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores from the Bayley Scales of Infant Development at 24, 30, and 36 months; and maternal self-esteem with the Spanish version of the Coopersmith Self-Esteem Inventory assessed at 24 months	Linear mixed effects regression model Sex, maternal age, maternal IQ, maternal education, parity, alcohol consumption, smoking, cohort, maternal self-esteem	Main effects of self-esteem and Pb on MDI and PDI repeated measures at 24, 30, and 36 months: *β* (SE), *p* Self-esteem: **MDI 0.24 (0.12), 0.04**; PDI 0.18 (0.12), 0.13 24 mon Pb: MDI -0.18 (0.14) 0.20; PDI -0.14 (0.14), 0.32 Adjusted relationship between childhood blood Pb with MDI and PDI scales at 24 months stratified by maternal self-esteem: β(SE), *p* Mental Development Index (MDI): **Lowest 3 quartiles self-esteem: -0.31 (0.15), p = 0.04** Highest quartile self-esteem: 0.36 (0.44), p = 0.44 p-value for interaction = 0.11 Quartile 1, low (n=145): -0.17 (0.25), p=0.50 Quartile 2 (n=148): -0.36 (0.25), p=0.15 Quartile 3 (n=178): -0.35 (0.44), p=0.39 Quartile 4, high (n=136): 0.38 (0.31); p=0.39 Psychomotor Development Index (PDI): Lowest 3 quartiles self-esteem: -0.25 (0.15), p = 0.10 Highest quartile self-esteem: 0.48 (0.40), p = 0.24 p-value for interaction = 0.21 Quartile 1, low (n=146): 0.21 (0.26); p=0.43 **Quartile 2 (n=147): -0.81 (0.23), p<0.01** Quartile 3 (n=178): -0.12 (0.33), p=0.71 Quartile 4, high (n=135): 0.50 (0.40); p=0.22	When mothers had low self-esteem, concurrent blood Pb was significantly associated with lower MDI and PDI score.
Prospective Tang (2008) Tongliang and Chongqing, China	110 children born to non-smoking Chinese women at one of three Tongliang county hospitals Year=2002 Male=49.1%	2 years	Cord 3.60 (1.59)	Child development measured by Gesell Developmental Schedules at 2 years of age presented as developmental quotients (DQ) in motor, adaptive, language and social areas.	Multiple regression; logistic regression Sex, gestational age, maternal education, environmental tobacco smoke (ETS)	Multiple regression analyses of GDS DQ scores at 2 years of age and cord Pb (β(95% CI): Motor: -3.72 (-7.98, 0.53); p=0.089 Adaptive: -3.59 (-9.20, 2.01); p=0.212 Language: -4.34 (-9.10, 0.43); p=0.077 **Social: -6.08 (-10.53, -1.63); p=0.009** **Average: -4.24 (-8.20, -0.29); p=0.038** Logistic regression analyses of GDS DQ scores at 2 years of age and cord Pb (OR(95% CI): **Motor: 3.85 (1.04, 14.25); p=0.043** Adaptive: 1.43 (0.43, 4.68); p=0.559 Language: 2.70 (0.70, 10.50); p=0.150 **Social: 7.29 (1.35, 39.45); p=0.021** Average: 4.25 (0.70, 25.89); p=0.116	Cord blood Pb was significantly associated with decrements in motor, social, and average developmental quotients.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Tellez-Rojo (2006) Mexico City, Mexico *Population may overlap with Surkan (2008), Gomaa (2002) and others*	294 children from 2 cohorts of the Harvard-Mexico Project on Fetal Pb Exposure, Risks and Intervention Strategies (FLERIS) with blood Pb levels < 10 µg/dL at both 12 and 24 months, Year=1994 – 2001 Male= 48%	12 months and 24 months	Cord blood = 4.85 (3.00) µg/dL 12 months = 4.27 (2.14) µg/dL 24 months = 4.28 (2.25) µg/dL	Development was assessed at 12 and 24 months by the Bayley Scales of Infant Development II (BSID II).	*t*-tests, Kruskal-Wallace test, χ^2 test, mixed-effects regression models, multivariate models, and linear regression models Mother's IQ, age and education; child's gender and birth weight.	Association between children's blood Pb levels at 24 months (<10 µg/dL) with MDI and PDI scores at 24 months **MDI: β=-1.04; p<0.01** **PDI: β=-1.18; p<0.01** Association between children's blood Pb levels at 12 months (<10 µg/dL) with MDI and PDI scores at 24 months MDI: NS **PDI: β=-3.0; p=0.01**	Concurrent blood Pb was significantly associated with lower MDI and PDI scores at 24 months, while blood Pb at 12 months was significantly associated with PDI, but not MDI, at 24 months.
Cross-sectional (Thomson *et al.* 1989) Edinburgh, Scotland *Population may overlap with Fulton (1987)*	501 children recruited from 18 primary schools in classes 3 and 4 in education authority primary schools in central Edinburgh. Year not stated, began in 1982 Male = 52%	6-9 years	Geom. mean: 10.4 (from Fulton (1987))	Behavior measured by the Rutter behavior scales, home interview with a parent	Multiple regression Child variables: age, sex, height, length of gestation, birthweight, medical history, days off school; Parent variables: mother's qualifications, working mother, parent's health, parent's mental health, smoking, parent's vocabulary, parent's matrices; Family variables: family history, birth order, family structure, parent/child communication, child's interest, parent participation; Household variables: car/phone owner, consumer goods owner, persons per room	Teachers' scores on log blood Pb: *β*; one-sided *p*-value **Total score: *β*=0.69; *p* =0.005** **Aggressive/anti-social: β=1.08; p=0.004** **Hyperactive: β=0.66; p=0.02** Neurotic: β=0.19; p=0.28 Parents' scores on log blood Pb: *β*; one-sided *p*-value Total score: *β*=0.38; *p* =0.06 Aggressive/anti-social: *β*=0.12; p=0.31 Hyperactive: *β*=0.39; *p* =0.07 Neurotic: *β*=0.33; *p* =0.08 Minimum of parents' and teachers' scores on log blood Pb: *β*; one-sided *p*-value **Total score: *β*=0.53; *p*=0.03** **Aggressive/anti-social: *β*=0.95; *p*=0.02** **Hyperactive: *β*=0.75; *p* =0.03** Neurotic: *β*=0.23; *p*=0.27	Concurrent blood Pb was significantly associated with teachers' ratings of behavior on aggressive/anti-social and hyperactive sub-scores and on total score, but not on the neurotic sub-score or parents' scores.
Prospective Tong (1996) Port Pirie, Australia	375 children living in and around the Pb smelting town of Port Pirie, South Australia, followed	mean not stated	Antenatal blood Pb: 10.1 (3.9) Cord Pb: 9.4 (3.9) Lifetime average	Children's intelligence quotient (IQ) measured at 11-13 years of age	Multivariate regression analyses	Regression of log blood Pb and IQ at age 11-13: β (SE) Cord blood: Verbal IQ: 1.0 (1.3); p=0.43 Performance IQ: 1.2 (1.8); p=0.48 Full scale IQ: 1.2 (1.5); p=0.41	Blood Pb levels measured at several ages after birth were significantly

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Population may overlap with Wigg (1988) and others	since birth; reevaluated at age 11-13; Year = 1979-1982 (at baseline) Male=48%		blood Pb at age 7: 17.8 (5.8) 6, 15, and 24 months; 2, 4, and 7 years			15 months: **Verbal IQ: -2.9 (1.3) ; p=0.03** Performance IQ:-0.6 (1.9); p=0.76 Full scale IQ:-1.8 (1.6) ; p=0.24 3 years: Verbal IQ:-2.6(1.6) ; p=0.11 Performance IQ:-4.2(2.3) ; p=0.07 **Full scale IQ:-3.8 (1.9) ; p=0.05** 5 years: **Verbal IQ:-3.7 (1.4) ; p=0.01** Performance IQ:-3.7 (1.9) ; p=0.06 **Full scale IQ:-4.0 (1.6) ; p=0.02** 7 years: **Verbal IQ: -2.8 (1.4) ; p=0.05** Performance IQ: -3.8 (2.0) ; p=0.06 **Full scale IQ: -3.4 (1.7) ; p=0.04** 11-13 years: Verbal IQ:-2.4 (1.3) ; p=0.06 Performance IQ:-2.0 (1.8) ; p=0.12 **Full scale IQ: -3.1 (1.7); ; p=0.04** Lifetime average to age 3: **Verbal IQ: -4.6 (1.9) ; p=0.03** Performance IQ: -3.2 (2.7) ; p=0.23 Full scale IQ:-4.3 (2.2) ; p=0.06 Lifetime average to age 5: **Verbal IQ: -5.0 (2.0) ; p=0.02** Performance IQ:-4.4 (2.8) ; p=0.10 **Full scale IQ: -5.1 (2.3) ; p=0.03** Lifetime average to age 7: **Verbal IQ: -4.3 (2.1) ; p=0.03** Performance IQ: -4.3 (2.9) ; p=0.14 Full scale IQ: -4.6 (2.4) ; p=0.06 Lifetime average to age 11-13: **Verbal IQ: -3.9 (1.8) ; p=0.03** Performance IQ: -4.7 (2.6) ; p=0.07 **Full scale IQ: -4.3 (2.1) ; p=0.04**	associated with verbal and/or full scale IQ at age 11-13.
Prospective Tong (1998) Port Pirie, South Australia *Population may overlap with Baghurst (1992) and others*	326 children living in and around the Pb smelting town of Port Pirie, South Australia, followed since birth; re-evaluated at age 11-13; Year = 1979-1982	All followed from birth until age 11-13	Age 2: 21.2 µg/dL Age 11-13 (n=326): 7.9 µg/dL	Bayley Mental Development Index (BMDI) at age 2, McCarthy General Cognitive Index (MGCI) at age 4, and IQs from the Wechsler Intelligence Scale for Children-	Multiple regression models ANOVA for association of changes in cognitive scores with grouped decreases in blood Pb Correlation between	By tertile of lifetime average blood Pb [Geometric Mean (SD) concurrent blood Pb (µg/dL)]: Mean Developmental Test score Age 2 BMDI Low (n=109) [12.5(1.2)]: 113.3 Middle (n=108) [18.5 (1.1)]: 109.9 Higher (n=109) [25.9 (1.1)]: 106.7 Age 4 MGCI Low (n=109) [13.3(1.2)]: 112.5	Blood Pb was associated with poorer performance on cognitive tests throughout childhood, even after mean Pb

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	(at baseline) %male not stated			(WISC) at ages 7 and 11-13	changes in IQ and declines in blood Pb (ungrouped) Adjusted for child's sex, birthweight, birth rank, feeding style during infancy, and duration of breast-feeding; maternal IQ and age at child's birth; socioeconomic status; Home Observation for Measurement of the Environment scores; and parental smoking habits and marital status	Middle (n=108) [19.5 (1.1)]: 107.3 Higher (n=109) [26.0 (1.2)]: 103.6 Age 7 WISC Low (n=109) [11.9(1.2)]: 109.9 Middle (n=108) [17.6 (1.2)]: 104.2 Higher (n=109) [22.8 (1.2)]: 101.4 Age 11-13 WISC Low (n=109) [11.0 (1.4)]: 104.3 Middle (n=108) [14.7 (1.3)]: 99.6 Higher (n=109) [18.6 (1.3)]: 96.9 <u>Change in IQ by decline in blood Pb (age 7 until 11-13)</u>: mean change in IQ points (95% CI) **<2.3 µg/dL: -5.4 (-3.8, -7.0)** **2.3-4.9 µg/dL: -5.0 (-3.2, -6.8)** **>4.9 µg/dL: -3.8 (-2.3, -5.3)** ANOVA >4.9 vs. <2.3: *P* = 0.45 <u>Change in cognitive function by decline in blood Pb (age 2 until 11-13)</u>: mean change in zScore (95% CI) <10.2 µg/dL: 0.03 (-0.15, 0.21) 10.2-16.2 µg/dL: 0.04 (-0.15, 0.23) >16.2 µg/dL: -0.01 (-0.20, 0.18) ANOVA >16.2 vs. <10.2: *P* = 0.74 <u>Change in cognitive function by decline in blood Pb (age 4 until 11-13)</u>: mean change in zScore (95% CI) <6.0 µg/dL: 0.05 (-0.12, 0.23) 6.0-10.3 µg/dL: 0.01 (-0.17, 0.18) >10.3 µg/dL: 0.01 (-0.17, 0.19) ANOVA >10.3 vs. <6.0: *P* = 0.42 Correlations between changes in blood Pb and cognitive function were weak and not statistically significant (data not shown). Strongest association: IQ and blood Pb decrease between ages 7 and 11 to 13: *r* = 0.12, *P* = 0.09	levels declined below 10µg/dL. Cognitive scores in those whose blood Pb levels declined the most were generally not improved relative to those who declined the least. Authors state that cognitive deficits from early childhood Pb exposure can only be partially reversed.
Cross-sectional Trope (2001) PA, USA	16 children with elevated blood levels compared to 5 non-exposed children who were siblings or cousins of exposed Year not stated Male (exp)=31% Male (unexp)=60%	Exposed: 8.75 years Unexposed: 8.5 years	Exposed: 39.93 (13.39) µg/dL Unexposed <10 µg/dL	Magnetic resonance spectroscopy (MRS) was used to evaluate the *in vivo* metabolism of the gray and white matter of the frontal cortex.	2-tailed unpaired Student's *t*-test; best fit linear regression. Covariates not reported	*N*-acetyl-aspartate/creatine and phosphocreatinine ratios in frontal gray matter (NAA/Cr ratio), mean (SD): Exposed= 1.10 (0.19) Unexposed = 1.30 (0.13) **p=0.035**	Pb exposed children had a significant decrease in the NAA/Cr ratio in frontal gray matter compared with the unexposed.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (μg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Cross-sectional van Wijngaarden (2009) Rochester, NY, USA	47 healthy subjects in Rochester, NY; Year =2008 Male=38.3%	61.55 (3) Range 55-67	Blood Pb not reported Bone: Calcaneus 6.1(8.5)μg/g Tibia 2.0(5.2)μg/g	Memory assessment with three tests (delayed-matching-to-sample-DMS; paired associate learning –PAL) in the of the Cambridge Neurophysiological Test Automated Battery (CANTAB) and Mild Cognitive Impairment measured with Montreal Cognitive Assessment (MoCA)	Spearman rank correlation, t-tests, continuity-corrected Wilcoxon-Mann-Whitney test, Multiple linear regression Age, education level, smoking status	Spearman rank correlation of CANTAB and MoCA by bone Pb excluding negative values (p-value): MoCA calcaneus Pb = -0.089 (0.58) MoCA tibia Pb = -0.059 (0.75) **DMS % correct all delays calcaneus Pb= -0.40 (0.0088)** **DMS % correct all delays tibia Pb= -0.43 (0.013)** **DMS % 12s delay calcaneus Pb= -0.34 (0.031)** **DMS % 12s delay tibia Pb= -0.42 (0.018)** PAL total errors adj. calcaneus Pb = 0.28 (0.082) **PAL total errors adj. tibia Pb = 0.42 (0.018)** **PAL stages completed calcaneus Pb = -0.43 (0.0056)** PAL stages completed tibia Pb = -0.19 (0.30) SRM % correct calcaneus Pb = -0.24(0.13) SRM % correct tibia Pb = 0.067(0.71) Adjusted within-group least-square means of cognitive test score (CANTAB) across bone Pb: DMS % correct all delays: Low calcaneus Pb = 86.94 (ref) Medium calcaneus Pb=86.36 (0.83) High calcaneus Pb = 80.85 (0.041); p = 0.07 p>0.1 when adjusted for hypertension p>0.1 for tibia Pb DMS % correct 12s delay: Low calcaneus Pb = 85.70 (ref) Medium calcaneus Pb=84.80 (0.83) High calcaneus Pb = 76.81 (0.051); p = 0.089 p>0.1 when adjusted for hypertension p>0.1 for tibia Pb Log PAL; total errors adjusted: Low calcaneus Pb = 2.36 (ref) Medium calcaneus Pb= 2.78 (0.23) High calcaneus Pb = 2.87 (0.18); p = 0.34 p>0.1 for tibia Pb	Tibia and calcaneus Pb were correlated with measures of memory impairment in 55-67 year olds. Calcaneus, but not tibia Pb, was borderline significant (p=0.07-0.09) for delayed matching to sample but adjusting for history of hypertension reduced the strength of the association
Case control Vinceti (1997) Northern Italy	15 ALS patients and 36 matched controls Year not stated Males: Cases=73% Controls=74%	mean not reported	Blood Pb (μg/dL): Controls: 10.8 (4.44) Cases: 12.7 (6.78)	Sporadic amyotrophic lateral sclerosis (ALS) and ALS severity scores. Blood Cd and Se also measured.	Student's t-test; Correlation; conditional logistic regression Matched by age and sex	<u>Difference in mean blood levels:</u> Pb: Controls 10.8; Cases 12.7; p = 0.383 <u>Relationship of blood Pb with ALS severity scores</u>: corr. Coeff; *P*-value Speech: -0.334; *P*=0.223 Swallowing: -0.236; *P*=0.398 Walking: -0.393; *P*=0.148 Dressing and hygiene: -0.334; *P*=0.224 Total: -0.440; *P*=0.101 Blood Cd was higher in ALS cases (*P*=0.025) but association with ALS diagnosis was not statistically significant (*P*=0.074)).	Blood Pb was not associated with ALS diagnosis or severity score.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Cross-sectional Walkowiak (1998) Germany	384 children aged 6 years in three German cities. Year=1994 %male not stated	6 years	Blood Pb at time of testing: 4.2 µg/dL 95th percentile: 8.9 µg/dL	Two subtests of the WISC (German version) vocabulary (V) and block design (BD) were combined to form a "WISC Index" which estimated IQ; Neurobehavioral Evaluation System 2 (NES2) used 5 subtests to assess motor speed, perceptual speed, reaction time, pattern memory functions, and sustained attention . *Also measured urinary Hg*	Multiple linear regression analysis Intelligence and contrast sensitivity in computerized testing	Multiple linear regression for Log blood Pb and WISC variables **WISC Vocabulary: b=-0.97; p<0.05** WISC Block Design: b=-0.43; NS WISC V+BD: b=-1.17; p<0.10 *Authors state that urinary Hg was not related to any of the neurological tests administered*	Concurrent blood Pb was significantly associated with lower scores on WISC Vocabulary test; Combined WISC index was borderline significant (p<0.1); and block design was not associated age 6 children.
Cross-sectional Wang (2002) Kaohsiung, Taiwan	934 third grade children from an area with known air and water pollution Year=1998-1999 Male= 51%	8.85 (0.41) years	5.50 (1.86) µg/dL	Child intelligence measured by ranking semester grades for Chinese (reading and writing short Chinese articles), Mathematics, History and Society, and Natural Science	Multiple regression analyses, Pearson correlation, Spearman correlation. Child's gender, father's age and socioeconomic status, mother's age and education.	<u>Correlations between class rankings and blood Pb:</u> Language (Chinese) **β(SE)= 0.37 (0.15); p < 0.05** History and Society **β (SE)= 0.43 (0.15); p < 0.05** Mathematics **β(SE) = 0.38 (0.16); p < 0.05** Natural Science **β (SE) = 0.32 (0.16); p < 0.05**	Concurrent blood Pb was significantly associated with lower child intelligence as measured by class rankings in four subjects.
Prospective Wang (2007) Boston, MA, USA *Population may overlap with Payton (1998) and others*	358 participants from the Normative Aging Study (NAS) for whom bone Pb measurements and cognitive function assessment data was available and who had been genotyped for *HFE* polymorphisms; Year=1991 – 2000 (initially enrolled in 1963) Male = 100%	67 years	Tibia: 19 µg/g Patella: 23 µg/g Measured beginning in 1991 and subsequently at 3-year intervals in a 6-year period	Cognitive function was assessed by the Mini-Mental State Examination (MMSE). Also genotyped for *HFE* polymorphisms	Multiple linear regression models Age, years of education, smoking, alcohol consumption, English as a first language, computer experience, diabetes.	Association with an interquartile (15µg/g) increase in tibia Pb biomarkers on change in MMSE score by class of *HFE* genotype <u>Binary model: Mean difference in annual rate of change in MMSE (95% CI):</u> Wild-type = -0.02 (-0.10, 0.07) **Any *HFE* variant allele = -0.22 (-0.39, -0.05)** **p-value interaction= 0.03** p-value trend: NA <u>Dose model: Mean difference in annual rate of change in MMSE (95% CI):</u> Wild-type = -0.02 (-0.10, 0.07) One *HFE* variant allele = -0.14 (-0.33, 0.04) **Two *HFE* variant alleles = -0.63 (-1.04, -0.21)** **p-value interaction: <0.01**	*HFE* polymorphisms significantly modified the association between tibia Pb and the rate of cognitive decline. Subjects with more copies of *HFE* variant alleles had greater cognitive

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						p-value trend: <0.01	decline per unit increase in tibia Pb.
Case-control Wang (2008) Anhui Province, China	1260 children, 4 – 12 years old from pediatric clinics at the Anhui Provincial Children's hospital and the Institute of Anhui Traditional Chinese Medicine: 630 ADHD cases pair-matched to 630 non-ADHD controls Years= 2003 – 2007; Male=69%	7.9 (2.1) years	ADHD = 8.77 (3.89) Control= 5.76 (3.39)	ADHD diagnosed from a structured diagnostic interview Modified to assess on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-R) criteria.	Pearson chi-square test; Student's *t*-test; conditional multiple variables logistical regression analyses with backward step-wise selection. Family history of ADHD, household composition, maternal tobacco use during pregnancy, maternal drinking during pregnancy, labor complications, cesarean delivery, perinatal distress, parents' age at birth, parents' education.	Logistical regression analysis of risk of ADHD by blood Pb: <u>Total sample</u> ≤ 5 µg/dL: reference **5 – 10 µg/dL: 4.92 (3.47, 6.99); p<0.01** **> 10 µg/dL: 6.00 (4.11, 8.77); p<0.01**	Concurrent blood Pb was significantly associated with risk of ADHD.
Cross-sectional Wang (2009) China	317 children in 1st to 6th grade from 4 rural villages in southeast China; Year = 2007 Male=51%	mean not reported Range=6-12	Blood =7.1(0.16) Urine=1.2(0.18) Hair=1.3(0.28) Nails=2.5(0.28) Measured when outcome assessed	Intelligence assessment (Revised Raven's Standard Progressive Matrices and converted to standardized intelligence scores from 0 to 100), ADHD (by Abbreviated Symptom Questionnaire of Conner's instrument for teachers), Pb symptoms (coryza dizziness, stomach ache or nausea), parental report of aggression	Student's t-test, Spearman's correlation, Binary or ordinal logistic regression Adjustments not described.	ADHD questionnaire filled in by school supervisors. Spearman's correlation coefficient of intelligence score: **Hair Pb r=0.51; p<0.01** **Urine Pb r=0.132; p<0.05** Blood and Nail Pb not reported *Binary regression* OR (95%CI) **Log Urine Pb OR= 1.79 (1.00,3.22) (*p<0.05*)** **Log Hair Pb OR=1.46 (1.06,2.03) (*p<0.05*)** *Logistic regression* OR (95%CI) **Log Urine Pb OR=1.28 (1.04-1.58) (*p<0.05*)** **Log Hair Pb OR=1.73 (1.18-2.52) (*p<0.05*)** Regression analysis and OR not reported for blood and Nail Pb data **Mental retardation** (intelligence scores below 25) rate was significantly higher (22.2%) in children with blood Pb above 10µg/dL than in those with lower blood Pb levels (9.4%) **p<0.05**). No association between Pb exposure and ADHD or Pb-related symptoms (dizziness, coryza, nausea, or aggressive behavior).	Urinary and hair Pb,but not blood or nail Pb were significantly associated with lower intelligence scores. Blood Pb was significantly associated with intelligence scores below 25 (cut-off for mental retardation) in 6-12 year olds;
Prospective Wasserman	392 infants, 208 from the Pb smelter	2 years	Total: Mid-pregnancy:	Mental Development Index (MDI), Bayley	Least squares regression analysis	Estimated change in 24-month MDI as blood Pb concentration increases from 10 to 30 µg/dl	Blood Pb at 2 years was

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
(1992) Kosovo, Yugoslavia *Population may overlap with Wasserman (1994)* and others	town of Kosovska Mitrovica and 184 from the unexposed town of Pristina; Year= initiated in 1985 Male=51.9%		13.1 (9.2) Cord: 14.4 (10.4) Exposed: Mid-pregnancy: 19.9 (7.7) Cord: 22.2 (8.1) Unexposed: Mid-pregnancy: 5.6 (2.0) Cord: 5.5 (3.3)	Scales of Infant Development	Gender, birth order, birth weight, ethnic group, HOME score, years of maternal education, maternal age, and maternal intelligence	Regression coefficient for log(blood Pb): β(SE) At birth (cord): -3.487 (2.262); p=0.1242 At 6 months: -2.373 (2.489); p=0.3412 At 12 months: -3.655 (2.654); p=0.1697 At 18 months: -3.719 (2.665); p=0.1640 **At 24 months: -5.307 (2.436); p=0.0301**	significantly associated with decrement in MDI at age 2, but early blood Pb levels were not statistically significant.
Prospective Wasserman (1994) Kosovo, Yugoslavia *Population may overlap with Wasserman (1992) and others*	332-338 infants from the Pb smelter town of Kosovska Mitrovica and the unexposed town of Pristina; Year=initiated in 1985 Male=48.5%	3 and 4 years	Mid-pregnancy: 13.0 (9.3) Cord: 14.1 (10.5)	Child developmental status at ages 3 and 4 years was assessed by the McCarthy Scales of Children's Abilities (MSCA) which provides a general measure of intellectual functioning (the GCI).	Least squares regression analysis Quality of the HOME environment; maternal age, intelligence, education, and language; birthweight and gender	Regression coefficients between blood Pb and the MSCA subscores at age 3-4: β(SE), p-value GCI Mid-pregnancy: -4.98 (2.76); p=0.072 **Cord: -7.14 (2.24); p=0.002** 6 months: -4.21 (2.36); p=0.076 **12 months: -7.53 (2.70); p=0.006** **18 months: -4.92 (2.50); p=0.05** **24 months: -10.44 (2.41); p=0.00** **30 months: -9.73 (2.59); p=0.00** **36 months: -9.25 (2.57); p=0.00** **42 months: -10.40 (2.63); p=0.00** **48 months: -9.43 (2.44); p=0.00** Perceptual Performance: **Mid-pregnancy: -4.70 (1.66); p=0.004** **Cord: -5.27 (1.36); p=0.00** 6 months: -2.39 (1.44); 0.099 **12 months: -4.38 (1.63); p=0.008** **18 months: -4.91 (1.54); p=0.002** **24 months: -6.76 (1.50); p=0.00** **30 months: -5.87 (1.62); p=0.00** **36 months: -6.92 (1.58); p=0.00** **42 months: -6.67 (1.68); p=0.00** **48 months: -7.06 (1.61); p=0.00** Verbal, Quantitative, Memory, and Motor were negatively but not significantly associated to MSCA	Blood Pb from cord, 12,18, 24, 30, 36, 42, and 48 months was significantly associated with a decrease in general intellectual functioning and the perceptual-performance subscale at age 3-4; mid-pregnancy blood Pb was also significantly associated with the perceptual-performance subscale; all other regression coefficients were negative but not statistically significant.
Prospective Wasserman (1997) Kosovo, Yugoslavia	309 7-year old children from the Pb smelter town of Kosovska Mitrovica and the unexposed	mean not reported Children were tested at 6.5,	Cord Blood: Pristina: 5.7 (3.6) Mitrovica: 23.2 (8.1) Blood Pb at 7yrs:	Wechsler Intelligence Scale for Children (WISC-III)	Ordinary least squares regression analysis. Gender, sibship size at the time of the IQ test, birth weight,	Association between Cumulative Pb and IQ at age 7: Est B (SE) β; p-value Full Scale IQ: -8.5864 (1.8868) **-0.2146; p < 0.001** Performance IQ: -9.1669 (2.0659), **-0.2177; p < 0.001** Verbal IQ -6.5931 (1.8611), **-0.1765; p < 0.001**	Cumulative Pb (7 years estimate from blood) was significantly

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Population may overlap with Wasserman (1992) and others	town of Pristina; Year=1984-1985 Male=50.2%	7.0, or 7.5 years of age.	Pristina: 8.0 (3.1) Mitrovica: 34.0 (11.0) Cumulative Pb exposure through age 7 (AUC7): Pristina: 0.87 (0.11) Mitrovica:1.52 (0.12)		hemoglobin concentration, language spoken in the home, HOME score, years of maternal education, maternal age, and maternal Raven's test score.	Authors state that a change in lifetime blood Pb from 10 to 30 µg/dL was associated with an estimated decrease in IQ: points (959% CI) Full Scale IQ: 4.3 points (3.4, 5.1) Verbal IQ: 3.4 points (1.7, 5.0) Performance IQ : 4.5 points (2.7, 6.3)	associated with lower Full Scale, Performance, and Verbal IQ scores at age 7.
Prospective Wasserman (1998) Kosovo, Yugoslavia *Population may overlap with Wasserman (1992) and others*	293 children from from the Pb smelter town of Kosovska Mitrovica and the unexposed town of Pristina; Year= 1985 – 1989 Male=51%	mean not reported Children were assessed at their 3-year visits.	Cord Blood: Pristina: 5.5 (3.4) Mitrovica: 22.0 (8.1) Blood levels at 36 months: Pristina: 9.8 (3.4) Mitrovica: 40.9 (14.9) Blood levels also assessed at 6, 12, 18, 24, and 30 months	Destructive and withdrawn childhood behavior measured using the Child Behavior Checklist (CBCL)	Hierarchical linear regression analysis. Town, residence type, gender, ethnicity, maternal education, HOME score, parity, child's IQ, fathers education.	Correlation between levels of reported behavior problems at age 3 and blood Pb levels: *ϐ* (SE), p-value Cord blood Pb: **Anxious-Depressed: β = 1.16 (0.58); p= 0.046** **Withdrawn: β = 1.52 (0.76); p= 0.046** **Sleep Problems: β = 1.00 (0.39); p= 0.011** Somatic problems: β = 1.14 (0.60); p= 0.058 Aggressive: β = 1.25 (0.85); p= 0.145 Destructive β = 0.79 (0.48); p= 0.097 36 months blood Pb: **Anxious-Depressed: β = 1.45 (0.72); p= 0.044** **Withdrawn: β = 3.07 (0.95); p= 0.001** **Sleep Problem: β = 1.09 (0.48); p= 0.024** **Somatic problems: β = 1.71 (0.70); p= 0.016** Aggressive: β = 1.85 (1.08); p= 0.089 **Destructive: β = 2.07 (0.61); p= 0.001** Authors state that blood Pb at 6, 12, 18, 24, and 30 months were inconsistently related to behavior problems.	Cord and 36 month blood Pb levels were significantly correlated with measures of behavioral problems in 3 year old children.
Prospective Wasserman (2000b) Kosovo, Yugoslavia *Population may overlap with Wasserman (1992) and others*	283 children from the Pb smelter town of Kosovska Mitrovica and the unexposed town of Pristina; Year=initiated in 1985, assessed in 1990-1992 % male not stated	54 months (4.5 years)	mean not reported Average $\log_{10}$ blood Pb concentration from birth through 54 months estimated	Motor skills assessed by the Bruininks Oseretsky Test of Motor Proficiency (consisting of 8 subtests); The Beery Test of Visual Motor Integration assessing motor functioning, fine motor composite, gross motor composite, and visual motor integration (VMI)	Multiple regression; least squares linear regression BMI, father's education, mother's education, HOME, residence type, sex, sibship size, birth weight, no lateralization, maternal Raven (IQ)	Regression of average $\log_{10}$ blood Pb concentration (birth through 54 months) and motor proficiency: β (SE) **Fine motor composite: -0.17 (0.68); p<0.005** Gross motor composite: 0.03 (0.80); p=ns **Visual motor integration: -0.24 (0.20); p<0.001**	Average lifetime blood Pb was significantly associated with lower fine motor and visual motor integration scores at age 4.5 years, but not gross motor scores.
Prospective Wasserman (2000a)	390 children from the Pb smelter town of Kosovska	Assessments from 3 to 7 years	Mid-pregnancy: 10.0 (2.09) Cord: 10.23 (2.29)	Early intelligence as assessed by McCarthy GCI at age	Repeated measures linear regression; generalized estimating	Adjusted associations between IQ, prenatal blood Pb and postnatal increments in blood Pb: B (SE) **Prenatal blood Pb: -6.05 (1.35); p<0.001**	Elevations in both prenatal and postnatal

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Kosovo, Yugoslavia *Population may overlap with Wasserman (1992) and others*	Mitrovica and the unexposed town of Pristina; Year=1985-1994 Male=51.8%	Mothers mean age at delivery 26.1 (4.6)	Average pre-natal: 10.23 (2.09) Average post-natal: Age 0-2: 13.18 (2.19) Age 2-3: 19.05 (2.14) Age 2-4: 19.50 (2.14) Age 2-5: 19.05 (2.14) Age 2-7: 17.34 (2.19) Converted from reported log_{10} Pb	3-4; Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R IQ) at age 5; and Wechsler Intelligence Scale for Children-version III (WISC-III IQ) at age 7	equation (GEE); HOME score, maternal age, intelligence, education, ethnicity, birthweight, and gender	**Postnatal blood Pb increase:** **Increase after age 2 (late): -1.78 (0.88); p<0.05** **Early and late postnatal increase: -2.71 (1.12); p<0.05** Authors state that the association between prenatal blood Pb and IQ is not linear; the strongest postnatal effects are noted at the lower levels of prenatal exposure.	blood Pb were significantly associated with small decrements in young children's IQ.
Prospective Wasserman (2001) Kosovo, Yugoslavia *Population may overlap with Wasserman (1992) and others*	199 children from the Pb smelter town of Kosovska Mitrovica and the unexposed town of Pristina; Year = recruited 1984-1985 and assessed 1989-1991; Male =51%	4-5	Cord: 5.6 (3.44) Average Pb (4 years): 7.24 (1.31) Measured semiannually from birth to the age of assessment (4, 4.5, or 5 years)	Child behavior problems were measured by the Child Behavior Checklist (CBCL): a Total Score and 8 log-transformed subscales, maternal smoking during pregnancy	Linear regression Age, smoking, HOME, birth weight, ethnicity, gender, maternal education	<u>Association between log cumulative blood Pb and log CBCL subscales</u>: β(SE) Aggressive: β(SE)= 0.08 (0.14); NS **Delinquent: β(SE)= 0.32 (0.15); p<0.05** Attention Problems: β(SE)= 0.06 (0.14); NS Thought Problems: β(SE)=0.27 (0.15); NS Social Problems: β(SE)= 0.11 (0.12); NS Anxious/Depressed: β(SE)= 0.19 (0.12); NS Somatic Complaints: β(SE)= 0.30 (0.17); NS Withdrawn: β(SE)= 0.22 (0.13); NS Maternal smoking during pregnancy was significantly positively associated with all subscales except Anxious/depressed or Somatic complaints	Average lifetime blood Pb was significantly associated with increased delinquency in 4-5 year olds; associations with other behavior subscales were positive but not statistically significant
Prospective Wasserman (2003) Kosovo, Yugoslavia *Population may overlap with Wasserman (1992) and others*	Children from the Pb smelter town of Kosovska Mitrovica and the unexposed town of Pristina; n=290 for blood analysis, n=167 for bone analysis Year=1986 – 1999 Male= 49% for blood analysis; 50% male for bone analysis	Blood Pb analysis: Pristina – 10.1 (0.1) and 12.2 (0.1) years Mitrovica – 10.1 (0.1) and 12.2 (0.2) years Bone Pb: Pristina – 11.88 (0.4) years Mitrovica – 11.96 (0.4) years	<u>Blood Pb</u> Pristina: Blood Pb: 6.1 (1.9) Concurrent tibia Pb (µg/g): 1.3 (6.6) Mitrovica: Blood Pb: 30.9 (9.6) Concurrent tibia Pb (µg/g): 39.1 (25.1) <u>Bone Pb subset</u> Pristina: Blood Pb: 6.0 (1.9) Concurrent tibia Pb (µg/g): 1.4 (6.5) Mitrovica: Blood Pb: 31.1 (9.9) Concurrent tibia Pb (µg/g): 40.1 (26.2) Measured every 6	Child intelligence measured by the Wechsler Intelligence Scale for Children (WISC–III): Full Scale IQ, Verbal IQ score and Performance IQ score at ages 10 and 12	Regression Modeling: repeated measures linear models; ordinary linear regression and a series of least squares regression models. Age, gender, sibship size at IQ test, birth weight, language, HOME score at age 9, maternal age, maternal education, maternal Raven score.	<u>Associations between average log_{10} blood Pb and IQ:</u> Full Scale IQ (age 10-12): *B* (SE), *p* Only adjusted for age: 0.90 (2.60) **Adjusted for other covariates: -5.31 (1.98), *p* < 0.01** Verbal IQ (age 10-12): *B* (SE), *p* Only adjusted for age: 0.65 (2.38) **Adjusted for other covariates: -4.84 (1.89), *p* < 0.05** Performance IQ (age 10-12): *B* (SE), *p* Only adjusted for age: 1.02 (2.71) **Adjusted for other covariates: -5.01 (2.13), *p* < 0.05** <u>Adjusted associations between log_{10} Pb and IQ (for those participating in bone Pb analyses):</u> Full Scale IQ (age 10-12): *B* (SE), *p;* standardized *β* **Model 1 (ave. blood): -5.02 (2.36), *p*<0.05; 0.1299** **Model 2 (tibia): -8.00 (2.29), p<0.01; 0.2076** **Model 3 (conc. blood): -4.48 (2.15), p<0.05; 0.1267** Model 4 (tibia x ave. blood): **Tibia: -11.16 (3.83), p<0.01; 0.2897** Ave. Blood: 3.97 (3.85), NS; 0.1027	Tibia Pb was statistically significantly associated lower full scale, verbal, and performance IQ at age 10-12. Average blood Pb was significantly associated with lower IQ scores as well, but was not statistically significant after controlling for tibia Pb in the smaller subset

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
			months (birth to 10 or 12)			Model 5 (tibia x conc. blood): **Tibia: -11.06 (3.76), p<0.01; 0.2871** Conc. Blood: 3.53 (3.43), NS; 0.0999 Verbal IQ (age 10-12): *B* (SE), *p;* standardized *β* Model 1 (ave. blood): -4.21 (2.22), *NS*; -0.1204 **Model 2 (tibia): -5.90 (2.18), p<0.01; -0.1694** Model 3 (conc. blood): -3.83 (2.02), NS; 0.1199 Model 4 (tibia x ave. blood): Tibia: -7.10 (3.65), NS; -0.2040 Ave. Blood: 1.51 (3.67), NS; 0.0433 Model 5 (tibia x conc. blood): Tibia: -6.92 (3.58),NS; -0.1989 Conc. Blood: 3.53 (3.43), NS; 0.0371 Performance IQ (age 10-12): *B* (SE), *p;* standardized *β* Model 1 (ave. blood): -5.11 (2.74), NS; -0.1209 **Model 2 (tibia): -8.88 (2.66), p<0.01; -0.2111** Model 3 (conc. blood): -4.52 (2.49), NS; 0.1170 Model 4 (tibia x ave. blood): **Tibia: -13.49 (4.44), p<0.01; -0.3207** Ave. Blood: 5.79 (4.48), NS; 0.1370 Model 5 (tibia x conc. blood): **Tibia: -13.40 (4.36), p<0.01; -0.3184** Conc. Blood: 5.21 (3.99), NS; 0.1348	with concurrent bone and blood Pb measures.
Prospective Weisskopf (2004) Boston, MA, USA *Population may overlap with Payton (1998) and others*	466 men in the Normative Aging Study; Year= 1993 – 2001 (initially enrolled in 1963) Male = 100%	67.4 (6.6) years	Patella = 23 µg/g Tibia = 19 µg/g Blood = 4 µg/dL	Cognitive decline was measured by the Mini-Mental State Examination (MMSE) scores	Generalized additive models, linear models; univariate and bivariate analyses.	Difference in change over time of MMSE score associated with one interquartile range (IQR) increase in Pb: Est. (95% CI) **Patella Pb (IQR = 20 µg/g): -0.24 (-0.44, -0.05)** Tibia Pb (IQR = 14 µg/g): -0.17 (-0.38, 0.04) Baseline blood Pb (IQR = 2 µg/dl): -0.01 (-0.13, 0.11)	Patella bone Pb was significnatly associated with a steeper decline over time in performance on the MMSE
Prospective Weisskopf (2007a) Boston, MA, USA *Population may overlap with Payton (1998) and others*	31 men from the Normative Aging Study: 15 from the lowest quartile of patella bone Pb and 16 from the highest quartile Year= 2002 – 2004 Male= 100%	Low exposure 73.2 (4.7) years High exposure 80.7 (6.1) years	Median patella Pb Low group: 9 (5 – 15) µg/g High group: 63 (43 – 86) µg/g Median tibia Pb Low group: 13 (9 – 17) µg/g High group: 41 (38 – 59) µg/g	Hippocampal levels of the metabolites N-acetylaspartate, myoinositol, and choline were assessed from Magnetic Resonance Spectroscopy (MRS) images taken ~ 6 years after Pb measured in bone.	Univariate analyses Age, renal insufficiency, diabetes, hypertension, and decline in bone Pb over time.	Effect estimate of 20 µg/g patella bone Pb concentration on myoinositol-to creatinine ratio in the hippocampus **0.09 (95% CI: 0.01, 0.17); p=0.03**	Cumulative patella Pb exposure is significantly associated with an increase in the myoinositol/creatinine ratio.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective and cross-sectional Weisskopf (2007b) Boston, MA, USA *Population may overlap with Payton (1998) and others*	1089 men in the Normative Aging Study; Year= 1993 – 2001 (initially enrolled in 1963) Male = 100%	68.7 (7.4) years	Median: Blood Pb: 5 µg/dL Patella: 5 µg/g Tibia: 20 µg/g	Participants were evaluated using: the Neurobehavioral Evaluation System 2 (NES2), the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Consortium to Establish a Registry for Alzheimer disease (CERAD) battery, the MMSE, and the developmental test of visual-motor integration (VMI).	Non-linear-spline regressions and linear repeated measures analysis; generalized extreme-studentized-deviation (ESD); ordinary least squares regression. Age, years between bone Pb measurements and date of first cognitive test, education, smoking, alcohol intake, number of years between the two tests, computer experience, English as a first language, quintile of physical activity.	Difference in cognitive test score per interquartile range (IQR = 3 µg/dL) increase in concurrent blood Pb: **Vocabulary** **-1.26 (-2.08, -0.44); p=0.003** Difference in change over time of visuospatial cognitive test scores per IQR increase in bone Pb: Patella (IQR = 20 µg/g): **Construction (# correct) -0.067 (-0.11, -0.02); p=0.0041** **Pattern (latency) 0.073 (0.04, 0.12); p=0.0008** **Pattern (# correct) 0.040 (0.002, 0.08); p=0.042** Tibia levels (IQR = 15 µg/g) Construction (# correct) -0.03 (-0.08, 0.02); p=0.22 **Pattern (latency) 0.079 (0.04, 0.12); p=0.0004** **Pattern (# correct) 0.042 (0.002, 0.08); p=0.038**	Concurrent blood Pb was significantly associated with lower vocabulary scores; cumulative bone Pb was significantly associated with declines in cognitive function over time, particularly visuospatial/ visuomotor subscales.
Case-control; Weisskopf (2010) Boston, MA, USA	330 Parkinson's disease (PD) patients in Boston, MA area and 308 acquaintance (spouse/in-law/friend), Normative Aging Study, and recruited controls; Years= 2003-2007 % Male= 65% PD 56% control	PD patients 66.5 (9.5) Control 69.4(8.8)	Tibia (µg/g) Q1-≤5 Q2 5.2-10.4 Q3 11.0-19.0 Q4 ≥19.1 No blood Pb data	Parkinson's disease (PD)	Logistical regression Age, age squared, sex, race, smoking, education, and recruitment site	Parkinson's disease and tibia bone Pb: OR (95% CI) All cases and Acq. and NAS controls (n=330/166) Q1 (<3.1µg/g): reference Q2 (3.5-9.6µg/g): 1.36 (0.70, 2.63) Q3 (10-17µg/g): 1.90 (0.90,4.01) **Q4 (>17.3µg/g): 3.21 (1.17, 8.83)** **p-trend = 0.02** Movement disorder clinics and Acq. controls(326/69) Q1 (<1µg/g): reference Q2 (1.7-7µg/g): 1.48 (0.72, 3.04) Q3 (7.8-13.1µg/g): 1.91 (0.91, 4.00) **Q4 (>13.9µg/g): 2.57 (1.11, 5.93);** **p-trend 0.03** All cases and all controls (330/308) Q1 (<3.1µg/g): reference Q2 (3.5-9µg/g): 1.30 (0.76, 2.23) Q3 (9.6-16µg/g): 1.37 (0.80, 2.36) **Q4 (>16µg/g): 1.91 (1.01, 3.60);** **p-trend 0.06** ORs for patella Pb were not statistically significant for any quartile (p-values for trend: 0.42, 0.47, 0.83)	Tibia Pb was significantly associated with a greater risk of Parkinson's disease, and patella Pb was not statistically significant.
Cross-sectional Weuve (2006) Boston, MA, USA	915 men in the Normative Aging Study with *ALAD*	68.7 *ALAD* 1-1	Blood Pb: 5.3 (1.23) *ALAD* 1-1: 5.3 (2.9) *ALAD*-2: 4.8 (2.7)	Cognitive functioning assessed by Mini-Mental State	Multivariable analyses Included interaction	Mean difference in MMSE score per IQR in Pb biomarker: Mean diff (95% CI) Blood Pb (adj for Set 1 covariates):	Higher blood Pb was significantly

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Population may overlap with Payton (1998) and others	genotype data. 149 ALAD-2 carriers and 766 wild-type non-carriers. Year= bone Pb assessed in 1991, cognitive testing began in 1993 (initially enrolled in 1963) Male = 100%	(n=766): 68.5 (7.3) *ALAD*-2 (n=149): 70.0 (7.4) 45-80 years at Pb assesment	Measured at time of cognitive testing Tibia Pb: *ALAD* 1-1: 21.7 (13.5) *ALAD*-2: 21.0 (11.1) Median: 19 µg/g Patella Pb: *ALAD* 1-1: 30.8 (19.7) *ALAD*-2: 29.7 (17.3) Median: 27 µg/g	Examination (MMSE), men began in 1993. *ALAD* rs1800435 polymorphism also genotyped.	term for blood Pb and ALAD-2 Set 1: Age at cognitive assessment, age-squared, years of education, computer experience, length of time between Pb and cognitive assessments, and timing of cognitive assessments. Set 2: all of Set 1 and smoking status, alcohol consumption, calorie adjusted calcium intake, regular energy expenditure on leisure time physical activity, and diabetes	**ALAD-2 carriers: -0.29 (-0.56, -0.02)** Wild-type: -0.05 (-0.16, 0.06) Difference in estimates: -0.24 (-0.53, 0.05) p-interaction=0.10 Blood Pb (adj for Set 2 covariates): ALAD-2 carriers: -0.26 (-0.54, 0.01) Wildtype: -0.04 (-0.16, 0.07) Difference in estimates: -0.22 (-0.51, 0.01) p-interaction=0.13 Tibia Pb (adj. for Set 1 covariates) ALAD-2 carriers: -0.20 (-0.62, 0.22) Wild-type: -0.07 (-0.23, 0.10) Difference in estimates: -0.13 (-0.58, 0.31) p-interaction=0.55 Tibia Pb (adj for Set 2 covariates): ALAD-2 carriers: -0.16 (-0.58, 0.27) Wildtype: -0.05 (-0.21, 0.12) Difference in estimates: -0.11 (-0.55, 0.33) p-interaction=0.63 Patella Pb (adj. for Set 1 covariates) ALAD-2 carriers: -0.28 (-0.66, 0.11) Wild-type: -0.08 (-0.24, 0.07) Difference in estimates: -0.19 (-0.60, 0.21) p-interaction=0.35 Patella Pb (adj for Set 2 covariates: ALAD-2 carriers: -0.26 (-0.64, 0.12) Wildtype: -0.07 (-0.23, 0.09) Difference in estimates: -0.19 (-0.59, 0.21) p-interaction=0.35	associated with poorer performance on the MMSE, among *ALAD-2* carriers. Associations between bone Pb levels and MMSE score did not vary by *ALAD-2* status.
Cross-sectional Weuve (2009) Boston, MA, USA	587 women from the Nurses Health Study; Years=1990-1994 and 2000-2004 Male=0%	61 Range 47-74	Blood: 2.9(1.9) Patella (µg/g) 12.6(11.6) Tibia (µg/g) 10.5(9.7) Bone Pb measured 5 years (on average) before outcome assessed	Cognitive assessment (by Telephone Interview for Cognitive Status-TICS),	Multiple linear regression Age and age-squared at Pb assessment, age at cognitive assessment, education, husband's education, alcohol consumption, smoking status, physical activity, aspirin use, ibuprofen use, use of vitamin E supplements, status of menopause, hormone use, Pb substudy source, and cognitive substudy source	Mean difference in overall standardized TICS score per SD increase in Pb (2µg/dL blood; 10µg/g tibia; 12µg/g patella): Blood Pb -0.015 (–0.069,0.039) (p =0.59) Patella Pb -0.012 (–0.056,0.033) (p=0.61) Tibia Pb -0.040 (–0.085,0.004) (p=0.08). Mean difference in overall standardized TICS score (excluding letter fluency) per SD increase in Pb (2µg/dL blood; 10µg/g tibia; 12µg/g patella): Blood Pb -0.016 (-0.071, 0.039) (p =0.57) Patella Pb -0.033 (-0.080, 0.014) (p=0.17) **Tibia Pb -0.051 (-0.099,-0.003) (p=0.04).**	Tibia Pb was associated with reduced cognitive function in older women; blood and patella Pb associations were not statistically significant.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Wigg (1988) Port Pirie, Australia *Population may overlap with Baghurst (1992) and others*	590 infants living in and around the Pb smelting town of Port Pirie, South Australia, followed since birth; evaluated at age 2; Year = 1979-1982 (at baseline) %male not reported	24 months	Geometric mean (95% CI) Cord: 8.3 (8.0, 8.6) 6 months: 14.4 (13.9, 14.8) 15 months: 20.9 (20.2, 21.5) 24 months: 21.2 (20.6, 21.8) Integrated postnatal: 18.1 (16.5, 19.6) Maternal exposure measured at 14-20 weeks and at delivery. Exposure measured at birth (umbilical cord)	Development as assessed by the Mental Development Index (MDI) and the Psychomotor Development Index (PDI) scores of the Bayley Scales of Infant Development	Pearson correlations; partial linear regression; blood Pb concentrations log-normally distributed Maternal age, father's secondary education, mother's secondary education, father's workplace, mother's workplace, parental relationship, mother's antenatal marital status, child's birth rank, neonatal oxygen use at birth, Apgar score at 5 minutes, neonatal jaundice, size for gestational age, mouthing activity at 15 moths, maternal IQ, and HOME score	<u>Correlations between blood Pb and age 2 Bayley scores</u>: <u>Maternal</u> 14-20 wks gestation: MDI=-0.06; PDI=-0.05 **After 20 wks gestation: MDI=-0.08 (p<0.05);**PDI=-0.02 **Average prepartum: MDI=-0.11 (p<0.05);** PDI=-0.06 At delivery: MDI=-0.03, PDI= -0.02 <u>Child</u> Umbilical cord: MDI=-0.04; PDI=-0.04 **6 months: MDI=-0.12 (p<0.05);** PDI=-0.07 **15 months: MDI=-0.12 (p<0.05);** PDI= -0.02 **24 months: MDI= -0.18 (p<0.01);** PDI=-0.02 **Integrated postnatal: MDI=-0.15 (p<0.01);** PDI=-0.01 <u>Partial linear regression coefficients for change in MDI at age 2 per unit change in blood Pb</u>: (adjusted model) β Average maternal antenatal: -0.07 Maternal at Delivery: 0.23 Cord: 0.10 6 months -0.16; p=0.07 **(unadj for HOME: -0.24, p =0.01)** **(unadj. for HOME and mat. IQ: -0.24, p =0.01)** 15 months: -0.03 24 months:-0.05 Integrated postnatal Pb: -0.12; p=0.19 **(unadj for HOME: -0.22, p =0.05)** **(unadj. for HOME and mat. IQ: -0.26, p =0.03)** Authors estimate that a child with PbB of 30 µg/dL at age 6 months will have a deficit of 3.3 points (approximately 3%) on the Bayley Mental Development Scale relative to a child with PbB of 10 µg/dl.	Blood Pb (maternal and postnatal) was significantly negatively correlated with MDI, but not PDI. Blood Pb at 6 months was associated with lower MDI scores, although not statistically significantly after adjusting for HOME score.
Cross-sectional Wright (2003) Boston,MA, USA *Population may overlap with Payton (1998) and others*	736 participants from the Normative Aging Study; Year=1991 – 2001 (initially enrolled in 1963) Male = 100%	68.2 (6.9) years	Patella = 29.5 (21.2) µg/g Tibia = 22.4 (15.3) µg/g Blood = 4.5 (2.5) µg/dL	Cognitive function was assessed by the Mini-Mental Status Exam (MMSE).	Multiple linear and logistic regression analyses. Age, education, alcohol consumption.	<u>AdjOR (95% CI) for a 1-unit change in blood, patella, or tibia Pb levels and a MMSE score below 24</u>: **Blood Pb: 1.21 (1.07, 1.36)** **Patella Pb: 1.02 (1.00, 1.03)** **Tibia Pb: 1.02 (1.00-1.04)**	Blood, patella, and tibia Pb are significantly associated with poor cognitive test performance in older men.
Prospective Wright (2008) Cincinnati, OH, USA	250 individuals recruited at birth from four prenatal clinics in the	19 - 24 years	Maternal = 8.3 (3.8) measured in 1st or early 2nd trimester:	Number of criminal arrests since turning 18 years of age	Negative binomial regression Maternal IQ, sex, SES	<u>Total arrest rates in young adults</u> <u>Rate Ratio (95% CI) for 5 µg/dL increase in blood Pb:</u> **Prenatal Pb: 1.40 (1.07-1.85)** Early childhood average Pb: 1.07 (0.88, 1.29)	Blood Pb was significantly associated with increased rates

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Population may overlap with Dietrich (1987) and others	Cincinnati Lead Study; Years: enrolled between 1979-1984 Male=50%		Early childhood avg.: = 13.4 (6.1) Age 6 (ave. 6.5): =8.3 (4.8)		using the Hollingshead Score, and maternal education level	**Age 6 Pb: 1.27 (1.03-1.57)** Violent crime arrest rates in young adults Rate Ratio (95% CI) for 5 µg/dL increase in blood Pb: Prenatal Pb: 1.34 (0.88, 2.03) **Early childhood average Pb: 1.30 (1.03, 1.64)** **Age 6 Pb: 1.48 (1.15, 1.89)** Non-Violent crime arrest rates in young adults Rate Ratio (95% CI) for 5 µg/dL increase in blood Pb: **Prenatal Pb: 1.40 (1.06, 1.84)** Early childhood average Pb: 1.05 (0.86, 1.28) Age 6 Pb: 1.22 (0.97, 1.53)	of arrests at age 19-24: total arrests (age 6 Pb & prenatal), violent crime arrests (early childhood and age 6 Pb), and non-violent crime (prenatal Pb only).
Prospective (Yuan *et al.* 2006) Cincinnati, OH, USA *Population may overlap with Dietrich (1987) and others*	42 young adults from the Cincinnati Lead Study (CLS); Birth Cohort Year= recruited in 1979-1984 Male=52%	21 (1) years	Mean childhood blood Pb from 3 months to 78 months: 14.18 (6.52) µg/dL Measured quarterly from birth until age 5 and at age 5.5, 6.0, and 6.5 years (78 months)	Functional magnetic resonance images were collected while the subject was performing a verbal generation task using a 3-plane gradient echo scan.	Pearson's correlation coefficient; regression coefficient; multiple regression analysis. Age, gender, full scale IQ, Hollingshead four-factor total SES (TOTSES), gestational age, birth weight, marijuana usage.	Partial correlation coefficient of the mean brain activation within regions of interest (ROI) and mean childhood blood Pb (birth to 6.5 years): partial *R*; *P* **ROI1 (left frontal – near Broca's): -0.32; p<0.04** **ROI2 (right temporal): 0.35; p<0.03** **ROI3 (left temporal – incl Wernicke's): -0.31; p<0.05** ROI4 (left frontal): partial *R* = -0.30; p =0.08	Childhood blood Pb levels were significantly correlated with brain reorganization associated with language function.
Cross sectional (Yule *et al.* 1984) London, England	166 children living near leadworks in outer London with measured blood Pb levels (pilot study). Year not stated % male not stated	8.6 years	13.52 (4.13) Range: 7-32 9 to 12 months before outcome assessed	Behavior measured by teacher ratings on Needleman's Scale, Rutter B(2) Questionnaire, and the Conners Scale.	Chi-square test; ANOVA and ANCOVA Social factors not controlled for	Percentage of children receiving a negative teacher rating on Needleman Scales of four blood Pb categories: 7-10, 11-12, 13-16, 17-32 µg/dL; χ^2 or *F*; *P*-value Distractible: 35.5, 35.4, 53.1, 45.7; χ^2=4.1; NS Not persistent: 2.9, 6.3, 12.2, 14.3; χ^2=3.8; NS Dependent: 14.7, 16.7, 28.6, 25.7; χ^2=3.4; NS Disorganized: 17.6, 12.5, 24.5, 20.0; χ^2=2.4; NS Hyperactive: 5.9, 2.1, 6.1, 0.0; χ^2=3.0; NS Impulsive: 5.9, 6.3, 22.4, 14.3; χ^2=7.5; *p* = 0.06 Easily Frustrated: 23.5, 20.8, 30.6, 17.1, χ^2=2.4; NS **Day dreamer:** **17.6, 25.0, 22.4, 48.6; χ^2=10.2 ; *p*=0.02** **Does not follow simple direction:** **5.9, 0.0, 0.0, 11.4; χ^2=10.3; *p*=0.02** **Does not follow sequence of direction:** **8.8, 10.4, 26.5, 25.7; χ^2=7.6; *p*=0.05** **Low overall functioning:** **14.7, 18.8, 18.4, 40.0; χ^2=8.2; *p*=0.04** Total score: 1.53, 1.54, 2.45, 2.63; F = 2.15; p=0.096 Percent 'deviant' on B(2) Scale of Rutter Questionnaire at two blood Pb levels: 7-12 and 13-32µg/dL; χ^2; *P*-value Restless: 26.8, 33.3; χ^2=0.55; NS Truants: 6.1, 0; χ^2=3.4; *p*=0.	Blood Pb was significantly associated with several measures of behavioral problems.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Squirmy: 13.4, 32.1; χ^2=7.21; *p*=0.007 Destroys: 3.7, 9.5; χ^2=1.46; NS **Fights: 6.1, 20.2; χ^2=6.04; *p*=0.014** Not liked: 11.0, 16.7; χ^2=0.70; NS Worried: 30.5, 35.7; χ^2=0.30; NS Solitary: 19.5, 26.2; χ^2=0.70; NS Irritable: 8.5, 15.5; χ^2=1.29; NS Miserable: 17.1, 16.7; χ^2=0.02; NS Twitches: 6.1, 9.5; χ^2=0.28; NS Sucks thumb: 1.2, 8.3; χ^2=3.16; *p*=0.08 Bites nails: 3.7, 11.9; χ^2=2.85; *p*=0.09 Absent: 14.6, 13.1; χ^2=0.00; NS Disobedient: 9.8, 21.4; χ^2=3.44; *p*=0.06 Can't settle: 14.6, 13.1; χ^2=2.19; NS Fearful: 28.0, 35.7; χ^2=0.80; NS Fussy: 17.1, 15.5; χ^2=0.0; NS Lies: 8.5, 16.7; χ^2=1.80; NS Steals: 1.2, 6.0; χ^2=1.48; NS Inert: 9.8, 20.2; χ^2=2.79; *p*=0.09 Aches: 13.4, 10.7; χ^2=0.09; NS Tears: 11.0, 4.8; χ^2=1.44; NS Stutters: 6.1, 9.5; χ^2=0.28; NS Resentful: 11.0, 15.5; χ^2=0.39; NS Bullies: 8.5, 14.3; χ^2=0.84; NS <u>Percent with Overactivity score of 3-6 of four blood Pb catagories:</u> 7-10, 11-12, 13-16, 17-32 µg/dL; χ^2; *P*-value **5.9%, 4.2%, 20.4%, 17.1%; χ^2= 8.12; P = 0.04** <u>Conner's factor score at two blood Pb levels – summaries of ANOVA and ANCOVA adjusted for age</u>: Mean 7-12 and 13-32µg/dL; *F*; *P*-value **Conduct problems: 0.04, 0.15; *F*=4.02; *p*=0.05** **Inattentive-Passive: 0.41, 0.62; *F*=5.68; *p*=0.02** Tension-Anxiety: 0.38, 0.41; *F*=0.52; *p*=0.47 **Hyperactivity: 0.27, 0.44; *F*=5.88 *p*=0.02** **Total Score: 0.26, 0.37; *F*=4.97; *p*=0.03**	
Cross sectional Zailina (2008) Malaysia	269 children from 2 urban schools in Kuala Lumpur (n=169), and one industrial-area school (n=100); Year not stated % male not stated	Urban area: 7.5 years Industrial area: 7.25 years Range: 6.5 to 8.5	Urban area = 3.75 Industrial area = 3.56	Cognitive ability measured by McCarthy Scales of Children's Abilities (MSCA)	General Linear Model test; correlation Parents' educational level, household income, number of siblings and their sequence in the family.	<u>Correlation between blood Pb levels and total cognitive score:</u> **Urban area: r = -0.140; p<0.05** **Industrial area: r = -0.197; p<0.05**	Concurrent blood Pb was significantly correlated with lower cognitive scores in 6-8 year olds in both urban and industrial areas.

Abbreviations: β-HCH - beta-hexachlorocyclohexane; δ-ALA - δ-aminolevulinic acid;
ACHIV - achievement standard score; ADHD – attention deficit hyperactivity disorder; Adj – adjusted; AFGS - auditory figure-ground subtest; Al - aluminum; *ALAD* – aminolevulinate dehydratase; ALS - amyotrophic lateral sclerosis; ANCOVA - analysis of covariance; ANOVA - analysis of variance; *APOE* – apolipoprotein E; As - arsenic;
BAEP - brainstem auditory evoked potential; BAER - brainstem auditory evoked responses; BASC - behavior assessment system for children; BASC-PRS - behavior assessment system for children, parent rating scale; BASC-TRS - behavior assessment system for children, teach rating scale; BD - block design subtest; BMI - body mass index; BOTMP - Bruinsinks-Oseretsky test of motor proficiency; BSI - Brief Symptom Inventory; BSID - Bayley scale of infant development; BTQ - Boston teachers questionnaire;
Ca – calcium; CANTAB - Cambridge neuropsychological testing automated battery; CAT - cognitive abilities test; CBCL - child behavior checklist; CBCL-EX - child behavior checklist, externalizing scale; CCTT - children's color trails test; CD - conduct disorder; Cd – cadmium; CDC – Centers for Disease Control and Prevention; CERAD - consortium to establish a registry for Alzheimer's disease; CES-D - Center for Epidemiologic Studies–depression scale; CI - confidence interval; CLS - Cincinnati Lead Study; CPMC - Columbia-Presbyterian Medical Center; CPRS - Connors parent rating scale; CPT - continuous performance test; CR - criminal record; CRS - Conners rating scale; CRS-CP - Conners rating scale, teacher rated, conduct problems; CS - contrast sensitivity; CSID - community screening instrument for dementia; CTBS - comprehensive test of basic skills; Cu – copper; CVLT - California verbal learning test;
DDE – dichlorodiphenyldichloroethylene; DDT – dichlorodiphenyltrichloroethane; DMS - delayed-matching-to-sample; DQ - developmental quotient; *DRD4* – dopamine receptor D4; DSM - diagnostic and statistical manual of mental disorders; DTI - diffusion tensor imaging;
ELEMENT - Early Life Exposures in Mexico to Environmental Toxicants; EOG - end of grade test; ERG – electroretinographic; ET – essential tremor; ETS – environmental tobacco smoke;
Fe – iron; FLERIS - fetal lead exposure, risks and intervention strategies; FSIQ - full scale intelligence quotient; FTII - Fagan test for infant intelligence; FWS - filtered word subtest; *HFE* – hemochromatosis;
GCI - general cognitive index; GEE - generalized estimating equations; GPA – grade point average;
Hg – mercury; HHANES - Hispanic Health and Nutrition Examination Survey; HOM - home observation for measurement of the environment; HR - hazards ratio; Hz – hertz;
ICD - international classification of disease; IQ – intelligence quotient;
K-ABC - Kaufman asssessment battery for children; KEDI - Korean Educational Development Institute; KID - Kent infant development scale; KiTAP – test battery for attention performance of children (German); K-SADS-E - Kiddie schedule for affective disorders and schizophrenia; K-TEA - Kaufman test of educational achievement;
MDI - mental developmental index; MGCI - McCarthy general cognitive index; MHDS-CD - mental health diagnostic schedule; MMSE - mini-mental state examination; Mn – manganese; MoCA - Montreal cognitive assessment; MPC - mental processing composite standard score; MRI - magnetic resonance image; MRS - magnetic resonance spectroscopy; MSCA - McCarthy scales of children's abilities; *MTHFR* – methylenetetrahydrofolate reductase;
NAA - N-acetyl aspartate; NAS - Normative Aging Study; NBAS - Brazelton neonatal behavioral assessment scale; NE-NCPP - New England cohort of the National Collaborative Perinatal Project; NES - neurobehavioral evaluation system; NHANES - National Health and Nutrition Examination Survey; NICU – neonatal intensive care unit; NONVB - non-verbal standard score; NPH - neighborhood psychosocial hazards; NS – not significant; NYS - National Youth Survey;
OR - odds ratio;
P – planning; PAL - paired associate learning; PAT - progressive achievement test; PCB - polychlorinated biphenyl; PD - Parkinson's disease; PDI - psychomotor development index; PDS - Prenatal Determinants of Schizophrenia study; PIQ - performance intelligence quotient; PPVT - Peabody picture vocabulary test; PRDB - parental report of predelinquent and delinquent behavior; PSS - Perceived Stress Scale;

RAVLT - Rey auditory verbal learning test; RLR - rule learning and reversal; ROCF - Rey-Osterrieth complex figure; RR - relative risk; RS - Rutter scale, aggressive/antisocial behavior;.

SAT - standard assessment test; SCAN - screening test for auditory processing disorders; SCL-90 - symptom checklist-90; SD – standard deviation; SDB - self-reported delinquent behavior scale; Se – selenium; SE – standard error; SEQ - sequential processing standard score; SES – socioeconomic status; SIM - simultaneous processing standard score; SRA - self-reported antisocial behavior; SRD - self-reported delinquency scale; SS - spatial span; SWM - spatial working memory;

tCr - total creatinine; TICS - telephone interview for cognitive status; TONI - test of non-verbal intelligence; TOSCA - test of scholastic abilities; TRF - teacher report form; TRF-DB - teacher report form, delinquent behavior scale; TRF-Ex - Teacher Report Form, Externalizing Scale;

UPSIT - University of Pennsylvania smell identification test;

VDR – vitamin D receptor; VEP - visual-evoked potentials; VIQ – verbal intelligence quotient; VMI - visual motor integration; VRM - visual recognition memory;

WAIS - Wechsler adult intelligence scale; WCST - Wisconsin card sorting test; WHO – World Health Organization; WIAT - Wechsler individual achievement test; WISC - Wechsler intelligence scales for children; WPIC-Ag - Walker problem identification checklist, teacher version, aggressive behavior scale;WPIC-P - Walker problem identification checklist, parent version, acting out scale; WPIC-T - Walker problem identification checklist, teacher version, acting out scale; WPPSI- Wechsler preschool and primary scales of intelligence scale for children; WRAML - wide range assessment of memory and learning; WRAT - wide range achievement test; WRAVMA - wide range assessment of visual motor activity;

Zn – zinc; ZPP – zinc protoporphyrin;

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