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The Relationship Between Blood Lead, Bone Lead and Child Intelligence

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ABSTRACT

We report associations between serial measures of blood lead and intelligence in children age 10–12 years, half heavily exposed to lead from the prenatal period onward, and half relatively unexposed. For a subsample, we examine bone lead-IQ associations, comparing them with blood lead associations. Both blood and bone lead levels were associated with intelligence decrements, small relative to the contribution of social factors. For each doubling of Tib-Pb, Full Scale, Performance, and Verbal IQ decreased by an estimated 5.5, 6.2, and 4.1 points, respectively. Bone lead-IQ associations were stronger than those for blood lead, which nonetheless provide robust analogues. Current BPb, easy to obtain, provides a useful means for assessing Pb exposure/IQ associations.

In most children, exposure to environmental lead (Pb) peaks early in life, yet the persistence of adverse associations between early Pb exposure and intellectual function into middle childhood remains a concern. Cumulative exposure to Pb in early life, assessed by the serial measurements of blood lead concentration (BPb), or BPb measured at age two, has been associated with decreased IQ scores at later ages (e.g., Bellinger et al., 1991; Bellinger, Stiles, & Needleman, 1992; Dietrich, Succop, Berger, Hammond, & Bornschein, 1991; McMichael et al., 1988; Tong, Baghurst, McMichael, Sawyer, & Mudge, 1996). For example, in Port Pirie, Australia, an estimated increase in average lifetime BPb from 10 to 20 μg/dl was associated with a 3-point decrease in WISC–R Full-Scale IQ at age 11–13, after adjustment for a range of potentially confounding variables (Tong et al., 1996). The strongest deficits were in subscales measuring "visual-motor coordination, attention, concentration and memory" (p. 1575), that is, the Information, Arithmetic, Block Design and Mazes subscales. In the Boston cohort (Bellinger et al., 1992) an increase in BPb from 10 to 20 μg/dl, measured at age 2, was associated with an estimated 5.3-point decrease in 10-year WISC–R Full-Scale IQ after adjustment for confounders. Although not formally tested, associations appeared strongest for verbal functioning.

In our previous work in the Yugoslavia cohort, BPb measured at single time points and average lifetime BPb were associated with modest decrements in intellectual function at ages 2, 4 and

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7 years, with stronger associations consistently noted for perceptual-motor functioning (Wasserman et al., 1997). At age 7 years, an increase in lifetime average BPb from 10 to 20 μg/dl was associated with an estimated 4.3-point decrease in WISC-III Full-Scale IQ and a 4.5-point decrease in Performance IQ.

These associations are based on estimations of Pb exposure using BPb, which reflects both current and cumulative exposure. The primary reservoir of lead is, however, skeletal, accounting for 90–95% of lead in the adult human body, and for approximately 70–80% of lead in children (Barry, 1981; Leggett, 1993; Schroeder & Tipton, 1968). Lead in the bone largely reflects cumulative exposure; the mobilization of lead from bone during times of rapid bone turnover (e.g. childhood, pregnancy and senescence) may represent a source of lead to target organs. The half-life of lead in bone is years, or even decades (Todd & Chettle, 1994). New technologies make the in vivo measurement of bone tibia lead (Tib-Pb) concentration feasible in large samples (Kosnett, Becker, Osterloh, Kelly, & Pasta, 1994; Schwartz, Stewart, Todd, Simon, & Links, 2000; Todd & Chettle, 1994). Indeed, associations between lead in tibia (Tib-Pb) and several health outcomes, including elevated blood pressure (Schwartz et al., 2000), decreased renal function (Roels et al., 1994), decreased hemoglobin concentration (Hu, Watanabe, Payton, Korrick, & Rotnitzky, 1994), and deficits in adult neurobehavioral function (Stewart et al., 1999) are stronger than the associations between BPb and these same outcomes.

Data on Tib-Pb levels in children are few and mostly are based on L-X-ray fluorescence (Rosen et al., 1991; Wieloploski et al., 1983), a method that measures Pb only on the bone *surface*. In contrast, the most widely used and validated technology, K-X-ray fluorescence, measures Pb in the full thickness of the bone (Hu, Rabinowitz, & Smith, 1998; Kim, Aro, Rotnitzky, Amarasiriwardena, & Hu, 1995). K-X-ray fluorescence technology uses a radioisotope of cadmium to fluoresce Pb X-rays from the bone and yields an estimate of Tib-Pb, expressed as micrograms of lead per gram of bone mineral (μg Pb/g).

There are several purposes to the present paper. First, we report associations between serial measures of BPb and intelligence in a cohort of children age 10–12 years, half of whom were heavily exposed to lead from the prenatal period onward, and half of whom were relatively unexposed. Because in ordinary clinical practice, neither serial BPb measurements nor Tib-Pb is usually available, we also report associations using a measure of current BPb. Second, in a subsample of children we consider the relationship between serial BPb measurements and Tib-Pb measured at age 12. Third, we report associations between Tib-Pb and intellectual functioning in that subsample of children. Finally, we compare associations between Pb exposure and intellectual functioning across measures of exposure estimation (i.e. current BPb [CBPb], serial BPb's or Tib-Pb).

This paper represents one of the first papers to identify predictors of Tib-Pb in children; data which would inform any theoretical comparisons do not yet exist. Comparisons among *different measures of exposure* are a priori but descriptive, rather than theory-driven. Associations among non-lead measures and child intelligence examined here are also descriptive, replicating as they do associations with similar models defined in earlier papers on associations between exposure and intelligence.

METHOD

The Yugoslavia Prospective Study of Environmental Lead Exposure is fully described in previous publications (e.g., Factor-Litvak, Wasserman, Kline, & Graziano, 1999; Graziano et al., 1990; Murphy et al., 1990; Wasserman et al., 1992). The children reside in two towns in Kosovo, Yugoslavia; one, Kosovska Mitrovica (Mitrovica), is the site of a lead smelter, refinery and battery plant, the other, Pristina, is relatively unexposed. Exposures cover a wide range, with BPb's ranging from 2 to 70 μg/dl. Between May 1985 and December 1986, women presenting for their first prenatal visits at two government sponsored clinics were asked to participate in a study of pregnancy outcomes. A total of 1502 women were recruited at mid-pregnancy, 602 in Mitrovica and 900 in Pristina; approximately 67% of women were recontacted after delivery in hospital. Infants were selected for follow-up based on umbilical cord BPb, town of residence and parental education. We excluded infants with gestation age <28 weeks or >44 weeks, those with central nervous system defects or chromosomal abnormalities, multiple births, and residence more than 10 km from either town's pediatric clinic. The cohort is well characterized as to exposure history, with BPb measured prenatally and every 6 months from birth onward. A total of 706 infants were selected for follow-up at 6-month intervals; of these the parents of 572 consented to at least one follow-up visit by age 12 years. Prospective follow-up of this cohort through age 12 took place between 1986 and 1999; bone lead assessments were conducted in the summer of 1998. All assessments were completed prior to the outbreak of war in Kosovo in 1999. The present analyses examine associations between lifetime Pb exposure and intellectual function at age 10–12 years.

Subjects

At age 12, 244 children were assessed; due to scheduling difficulties, however, 8 children were almost 13 years old. The remainder were between 11 years 8 months and 12 years 8 months, and most ($n = 196$) were between 12 years and 12 years 4 months. For 69 children whose IQ was not assessed at age 12, we use IQ from the age 10 assessment, bringing the total sample with IQ measures at age 10–12 to 313.

We measured Tib-Pb between the ages of 11–13 years. Logistical and cost constraints limited the number of children for whom we could measure Tib-Pb. Thus, we selected a subsample with a broad range of exposures, from among those with the most (8 or more) serial BPb assessments prior to the time of Tib-Pb measurement. The subsample included 209 children; 111 and 98 from Mitrovica and Pristina, respectively.

All procedures were approved by Institutional Review Boards at Columbia Presbyterian Medical Center and the University of Pristina. Approval for the bone lead assessments was also obtained from the Institutional Review Board at the Mount Sinai School of Medicine. Parental written informed consent and the assent of each child were obtained.

Procedure

All interviews and other assessments were translated into the two dominant languages of the region (and back-translated into English). At mid-pregnancy, delivery, and at subsequent 6-month intervals, mothers were interviewed by trained bilingual (Serbo-Croatian and Albanian) nurses regarding child and family health, and sociodemographic characteristics. Children underwent regular developmental assessments, when height, weight and measures of other health outcomes were obtained.

Venous blood samples were obtained for measuring BPb (Fernandez & Hilligoss, 1982), erythrocyte protoporphyrin (EP: Piomelli, 1973), serum ferritin (SF: Miles, Sipschitz, Bieter, & Cook, 1974) and hemoglobin (Hgb). Whole blood and serum samples were appropriately stored and transported to Columbia University where the laboratory participates in the BPb and EP quality control programs of the Centers for Disease Control and Prevention. Over the course of the study, intraclass correlation coefficients between our laboratory's values and samples calibrated at CDC ranged between .97 and .99.

Tibial bone lead (Tib-Pb) was measured using ^{109}Cd based K-shell-X-ray fluorescence (Todd & Chettle, 1994); details of the technology employed in the current study have been previously described (Todd et al., 2001). Measurement uncertainty with this procedure is comparable to that observed in adults, using previous generation nuclear electronics. With our instrumentation, the minimum detectable Tib-Pb was 4 μg Pb/g bone mineral (i.e., three times the standard deviation of repeated measures of a blank sample). For Tib-Pb concentrations close to or below this limit, the instrumentation occasionally records negative values. This results from production of an unbiased point estimate of Tib-Pb that oscillates around the true Tib-Pb value. In the present sample, Tib-Pb measurements ranged between -14.4 and $+193.5\,\mu$g Pb/g bone mineral. Previous investigations of the use of negative values of Tib-Pb (Hu et al., 1998; Kim et al., 1995) suggest that their retention in analyses is useful since alternative procedures, such as recoding them to "0" or to a multiple of the standard deviation of the background noise, introduce bias. We performed our analysis twice, once retaining the negative values and once adding a constant of 15 to eliminate negative values when the logarithmic transformation was employed; this transformation was undertaken to make the distributions approximately symmetrical. Results from both analyses were comparable and we report analyses using the latter algorithm.

Measures

Child Intelligence

At ages 10 and 12, intelligence was assessed using the Wechsler Intelligence Scale for Children -III (Wechsler, 1991). This recently re-standardized, individually administered, test has good reliability and validity. The *WISC-III* consists of five (or six, depending upon administration) verbal subtests that provide a Verbal IQ score, and a similar number of performance subtests that together provide a Performance IQ score (Wechsler, 1991). Because translated vocabulary items often have different secondary meanings in different languages, consistent with our earlier work (Wasserman et al., 1997), we did not administer the Vocabulary subtest, and administered five verbal subtests (Information, Similarities, Arithmetic, Comprehension, and Digit Span). We administered five performance subtests (Picture Completion, Coding, Picture Arrangement, Block Design and Object Assembly). When these data were collected, neither the WISC-III, nor any other widely used IQ test had been standardized for either Serbian or Albanian children. Because our analyses essentially predicted rank-order IQ scores, the lack of Yugoslav norms was not a limitation. The WISC-III, as well as other measures used here but not formally normed in Yugoslav populations, nonetheless showed expectable associations with other study measures.

Quality of the Home Environment

Between ages 9 and 10, an adaptation of the elementary age Home Observation for the Measurement of the Environment (HOME) was administered as a structured interview during a home visit. The HOME is a strong predictor of childhood intelligence (e.g., Bradley et al., 1989). For the 9 children for whom the HOME was not administered between ages 9 and 10, we estimate HOME score from the preschool version administered at age 3 years. In the 374 children with HOME assessments at both 3 and 9–10 years, the correlation for total score was 0.54 ($p < .0001$). Results from regression analyses were similar when we excluded the 9 children without recent HOME assessments from analysis.

Maternal Intelligence

The Raven's Standard Progressive Matrices (Raven, Court, & Raven, 1983), a non-verbal test relatively free of cultural influences, was used to estimate maternal intelligence.

BPb

Cumulative lifetime exposure to Pb was first estimated using the average of BPb measurements obtained at 6-month intervals from birth to the age of outcome assessment, that is, ages 10 or 12. The distribution of BPb is skewed; therefore we used a base 10 logarithmic transformation. Because BPb's measured at close intervals are highly correlated in this population (Factor-Litvak et al., 1999), for children missing BPb at some age, AvLog_{10} BPb was calculated based on all available data. We sought to maximize the number of children included in these analyses. Thus, for 100 children missing BPb at the time of the final IQ assessment, we substituted a BPb value from a visit at ±6 months (age 10 years) or ±12 month (age 12 years). Our analyses excluded 36 children without a BPb measured within this time window. We refer to this measurement below as AvLog_{10} BPb10/12. For 150 children who provided a blood sample within 3 months of the bone lead measure, we estimate concurrent BPb (CBPb).

Statistical Analysis

Missing Data

Analyses of Verbal or Performance IQ required complete data on four of five subtests; for Full Scale IQ, both Verbal and Performance IQ were required. One child, determined during the course of the study to have a substantial unremediated hearing impairment, was excluded from analyses predicting Verbal and Full Scale IQ. Covariate information (in most cases, either HOME or maternal Raven score, or both) was missing on 23 children; these children were omitted from the regression analyses.

Regression Modeling

Repeated measures linear models were used to estimate the associations between average lifetime BPb and Full Scale IQ, Verbal IQ and Performance IQ measured at ages 10 and 12, adjusting for potential confounders. Covariates, defined in our previous work with this cohort, included: age, gender, sibship size at the time the IQ test was administered, birth weight, language spoken in the home (Albanian, Serbian, other), HOME score, maternal age, maternal years of schooling, and maternal Raven score. All parameters were estimated using the generalized estimating equations (GEE) approach (Liang & Zeger, 1986), which accounts for within subject correlations while using all available data.

Ordinary linear regression was used to estimate the associations between predictor variables and the log (base 10) transformation of Tib-Pb. We considered the following potential predictors: concurrent BPb (measured at the time of Tib-Pb measurement), gender, age, ethnicity, place of residence relative to the industrial Pb complex, maternal education, anthropometric measures (height, weight, shoulder width, tibia length and width, calf circumference and skinfold thickness) and HOME score. Separate models were fit for children in each town. The final town-specific models were obtained using a backward elimination procedure that retained continuous variables with $p < .05$ and sets of indicators corresponding to categorical variables if at least one indicator in each set was statistically significant at $p < .05$. The procedure concluded when no additional variables met these criteria. Finally, in order to adjust for uncertainty in the Tib-Pb measures, the error term associated with each measurement was included in the model. Using the above criteria, gender, tibia width, and calf circumference were controlled in the model for

Pristina and tibia length and height were controlled in the model for Mitrovica.

In the clinical management of lead exposure, retrospective serial measurements of BPb are rarely available. In order to contrast Tib-Pb associations with the kind of information generally available to clinicians, we performed a series of least squares regression models including Tib-Pb and measures of BPb, separately and together: (a) CBPb; and (b) AvLog$_{10}$ BPb10/12. We then compared the strength of the associations for each measure of exposure.

RESULTS

Sample Characteristics

Overall, 290 children were included in analyses of BPb and IQ, and 167 children in analyses of Tib-Pb and IQ. Characteristics of the children included in these analyses are presented in Table 1, separately by town. Mothers from Mitrovica achieved higher Raven's scores [for BPb and Tib-Pb analyses, respectively,

Table 1. Characteristics of Those Included in the BPb and Bone Analyses (Avlog$_{10}$ BPb), by Town.

	Blood Pb analysis		Bone Pb analysis	
	Pristina ($N = 146$)	Mitrovica ($N = 144$)	Pristina ($N = 86$)	Mitrovica ($N = 81$)
Males	49.3%	49.3%	53.5%	45.7%
Ethnicity				
Albanian	68.5%	52.8%	74.4%	68.0%
Serbian	25.3%	42.4%	20.9%	29.6%
Other	6.2%	4.9%	4.7%	2.5%
	Mean ± *SD*			
Age				
10 years	10.1 ± 0.1	10.1 ± 0.1	–	–
12 years	12.2 ± 0.1	12.2 ± 0.2	11.88 ± 0.4	11.96 ± 0.4
HOME score	37.6 ± 7.7	39.3 ± 8.9	36.8 ± 7.5*	39.8 ± 8.3
Birth order	2.1 ± 0.7	1.8 ± 0.8	2.0 ± 0.7	2.0 ± 0.8
Birth weight (kg)	3.3 ± 0.5	3.3 ± 0.5	3.4 ± 0.5	3.4 ± 0.5
Mother's age	26.5 ± 4.8	26.7 ± 5.3	26.5 ± 4.9	27.5 ± 5.3
Maternal intelligence	29.8 ± 12.9*	35.1 ± 12.5	29.6 ± 12.7*	33.6 ± 12.0
Mother's education	9.0 ± 3.8	9.4 ± 3.6	8.9 ± 4.0	9.1 ± 3.6
Avlog(BPb)[a]	0.8 ± 0.1*	1.5 ± 0.1	0.8 ± 0.1*	1.5 ± 0.1
Concurrent BPb[b]	6.1 ± 1.9*	30.9 ± 9.6	6.0 ± 1.9*	31.1 ± 9.9
Tib-Pb[c]	1.3 ± 6.6*	39.1 ± 25.1	1.4 ± 6.5*	40.1 ± 26.2
Full Scale IQ				
Age 10	75.9 ± 14.2	76.8 ± 14.9	–	–
Age 12	75.4 ± 14.3	75.9 ± 14.2	75.1 ± 13.3	75.3 ± 14.0
Performance IQ				
Age 10	76.0 ± 15.0	77.2 ± 16.4	–	–
Age 12	77.6 ± 15.0	78.0 ± 15.4	77.4 ± 14.3	77.3 ± 15.5
Verbal IQ				
Age 10	79.7 ± 13.3	80.3 ± 13.2	–	–
Age 12	77.1 ± 12.9	77.6 ± 13.0	76.8 ± 12.1	76.7 ± 12.6

Note. [a] Average of the log$_{10}$ serial blood leads.

[b] Blood lead measured at time of bone lead assessment.

[c] Bone lead.

*Significant difference across towns, at $p < .05$.

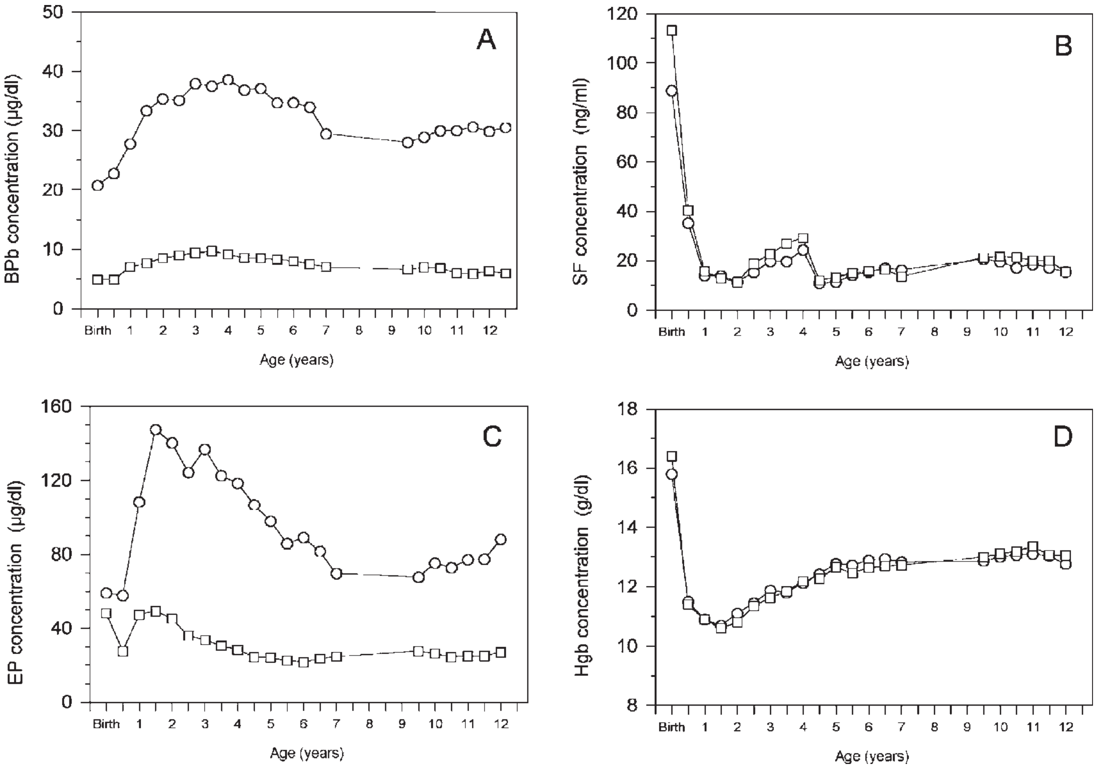

Fig. 1. Hematologic findings for children in Mitrovica (□) and Pristina (○) through age 12 years. (A) BPb; (B) SF; (C) EP; (D) Hgb.

$t_{(288)} = 3.55$, $p < .01$, $t_{(165)} = 2.09$, $p < .05$]. For children included in the bone lead analysis, HOME scores were higher in Mitrovica than in Pristina ($t_{(165)} = 2.41$, $p < .05$). Except for the expected differences in BPb and Tib-Pb, there were no other differences across towns.

Compared to those not included in analyses of BPb and Tib-Pb, included children had higher HOME scale scores [for BPb, 38.45 vs. 32.25, $t_{(466)} = 7.65$; for Tib-Pb, 38.23 vs. 34.36, $t_{(396)} = 4.62$, p's $< .01$]. Compared to those not included, children included in the analyses of Tib-Pb had slightly older mothers [27.0 vs. 25.9, $t_{(570)} = 2.40$, $p < .05$] and lower concurrent BPb [18.2 vs. 24.6 µg/dl, $t_{(202)} = 2.53$, $p < .05$]. Included samples were otherwise comparable to the larger sample (data not shown).

Hematalogic Findings

Mean values for BPb, EP, Hgb, and serum ferritin are plotted against age (through 12 years) in Figure 1(a–d). As expected, BPb and EP are higher in children in Mitrovica. In both towns, hematologic measures have remained relatively stable since early childhood.

Blood Lead and Intelligence

As in our prior work, socio-demographic variables were related to intelligence in the expected directions. For example (Table 2), children with higher Full Scale IQ scores at ages 10–12 were more likely to be to have been heavier at birth, of Serbian ethnicity, and from more organized homes. Their mothers were more likely to have been older, more educated and they achieved higher Raven's scores.

As Table 2 shows, before adjustment for covariates other than age, Avlog$_{10}$ BPb was unrelated to Full Scale IQ/10–12, to Verbal IQ/10–12, or to Performance IQ/10–12. After covariate adjustment, Avlog$_{10}$ BPb was significantly and negatively related to all components of IQ measured at ages 10 and 12 years. A doubling of the average

Table 2. Associations [Estimated $B \pm SE(B)$] Between Avlog$_{10}$ BPb and Components of IQ, Before and After Covariate Adjustment.

	Full Scale IQ/10–12	Verbal IQ/10–12	Performance IQ/10–12
Adjusted for age only			
Avlog$_{10}$ BPb[a]	0.90 ± 2.60	0.65 ± 2.38	1.02 ± 2.71
After covariate adjustment			
Age	-0.01 ± 0.29	$-0.90 \pm 0.28^{**}$	$0.80 \pm 0.35^{*}$
Serbian versus Albanian	$8.22 \pm 1.64^{**}$	$8.71 \pm 1.59^{**}$	$6.53 \pm 1.73^{**}$
Other versus Albanian	-3.16 ± 2.47	-3.68 ± 2.13	-1.72 ± 2.84
Birth Order	-1.48 ± 0.81	-1.07 ± 0.76	-1.58 ± 0.89
Birthweight (kg)	$3.82 \pm 1.35^{**}$	$2.77 \pm 1.32^{*}$	$4.31 \pm 1.45^{**}$
Boy versus girl	1.12 ± 1.24	2.03 ± 1.15	0.19 ± 1.40
HOME score	$0.37 \pm 0.08^{**}$	$0.33 \pm 0.08^{**}$	$0.35 \pm 0.09^{**}$
Maternal age	$0.34 \pm 0.12^{**}$	$0.28 \pm 0.12^{*}$	$0.36 \pm 0.14^{**}$
Maternal education	$0.58 \pm 0.21^{**}$	$0.49 \pm 0.18^{**}$	$0.58 \pm 0.24^{*}$
Maternal IQ	$0.34 \pm 0.06^{**}$	$0.24 \pm 0.06^{**}$	$0.39 \pm 0.06^{**}$
Avlog$_{10}$ BPb	$-5.31 \pm 1.98^{**}$	$-4.84 \pm 1.89^{*}$	$-5.01 \pm 2.13^{*}$

Note. [a] Average of the log$_{10}$ serial blood leads.
$^{*}p < .05$; $^{**}p < .01$.

Table 3. Social and Demographic Determinants of Bone Lead Concentration.

	Pristina			Mitrovica		
	N	Mean Tib-Pb[a]	*SD*	*N*	Mean Tib-Pb[a]	*SD*
Total sample	98	1.36	6.5	111	39.09	24.55
Sex						
Male	52	2.89	6.87	55	42.14	29.76
Female	46	−0.39	5.64	56	36.10	17.82
Ethnicity						
Albanian	72	1.41	6.39	67	37.80	27.00
Serbian	21	0.08	6.37	40	40.29	20.89
Other	5	5.86	7.99	4	48.73	14.29
Address at birth relative to factory						
Within 2 km	0	–	–	90	42.32	25.53
2–4 km	1	4.4	–	5	38.40	18.59
4–6 km	0	–	–	14	23.28	5.04
6–8 km	0	–	–	2	6.20	1.27
>8 km to Pristina	7	−1.93	7.07	0	–	–
Pristina	90	1.57	6.46	0	–	–
Maternal education						
None	5	2.86	7.58	8	43.19	29.40
1–8 years	42	0.61	6.16	50	41.40	30.75
9–12 years	43	2.00	7.21	46	36.66	16.19
≥13 years	8	0.81	3.48	7	33.86	14.62

Note. [a] Bone lead, in µg Pb/g bone mineral.

lifetime BPb (e.g. an increase in BPb from 3 to 6 µg/dl or from 10 to 20 µg/dl) was associated with a decrease in Full Scale, Performance, and Verbal IQ of 1.6, 1.5, and 1.5 points, respectively.

Predictors of Bone Lead

As expected, Tib-Pb was significantly higher in Mitrovica compared to Pristina, and higher in those children with residence at birth closest to

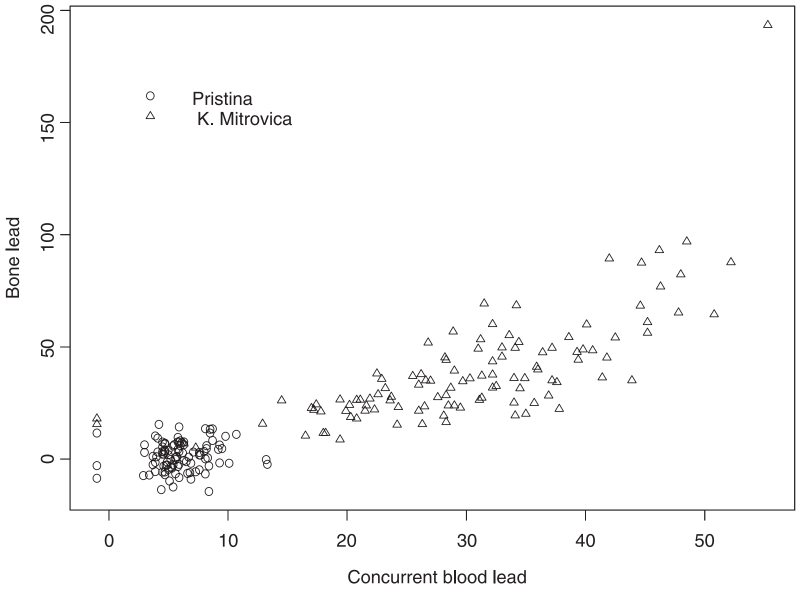

Fig. 2. Associations between concurrent blood lead and bone lead.

Table 4. Associations Between Blood Lead, Bone Lead and Components of IQ, After Covariate Adjustment, for Those Participating in Bone Lead Analyses.

	Full Scale IQ ($n = 166$)		Verbal IQ ($n = 166$)		Performance IQ ($n = 167$)	
	Estimated $B^a \pm SE(B)$	β^b	Estimated $B \pm SE(B)$	β	Estimated $B \pm SE(B)$	β
Analysis 1:						
Avlog$_{10}$ BPb[c]	$-5.02 \pm 2.36^*$	0.1299	-4.21 ± 2.22	−0.1204	-5.11 ± 2.74	−0.1209
Analysis 2:						
Log$_{10}$ Tib-Pb[d]	$-8.00 \pm 2.29^{**}$	0.2076	$-5.90 \pm 2.18^{**}$	−0.1694	$-8.88 \pm 2.66^{**}$	−0.2111
Analysis 3:						
Log$_{10}$ CBPb[e]	$-4.48 \pm 2.15^*$	0.1267	-3.83 ± 2.02	0.1199	-4.52 ± 2.49	0.1170
Analysis 4:						
Log$_{10}$ Tib-Pb	$-11.16 \pm 3.83^{**}$	0.2897	-7.10 ± 3.65	−0.2040	$-13.49 \pm 4.44^{**}$	−0.3207
Avlog$_{10}$ BPb	3.97 ± 3.85	0.1027	1.51 ± 3.67	0.0433	5.79 ± 4.48	0.1370
Analysis 5:						
Log$_{10}$ Tib-Pb	$-11.06 \pm 3.76^{**}$	0.2871	-6.92 ± 3.58	−0.1989	$-13.40 \pm 4.36^{**}$	−0.3184
Log$_{10}$ CBPb	3.53 ± 3.43	0.0999	1.18 ± 3.27	0.0371	5.21 ± 3.99	0.1348

Note. [a] Unstandardized regression coefficient.
[b] Standardized regression coefficient.
[c] Average of the log$_{10}$ serial blood leads.
[d] Log$_{10}$ Bone lead.
[e] Log$_{10}$ Blood lead measured at time of bone lead assessment.
$^*p < .05$; $^{**}p < .01$.

the lead industrial complex (Table 3). Few social or demographic variables were associated with Tib-Pb. Boys had slightly higher Tib-Pb than did girls. In Mitrovica, Tib-Pb decreased with increasing maternal education and decreased with higher scores on the HOME scale ($r = -.23$, $p = .01$). These relationships were not found in Pristina.

As Figure 2 shows, concurrent BPb was strongly and positively associated with Tib-Pb in Mitrovica (Spearman $r = .75$, $p < .01$) but not in Pristina ($r = .15$). Similar associations were found between average lifetime BPb, and Tib-Pb, with correlation coefficients of .85 and .11 in Mitrovica and Pristina, respectively.

Bone Lead, Blood Lead, and Intelligence

We next compared the relative strengths of the associations between exposure, based on BPb and Tib-Pb, and IQ. For children with both available

Figure 3a. Tib-Pb

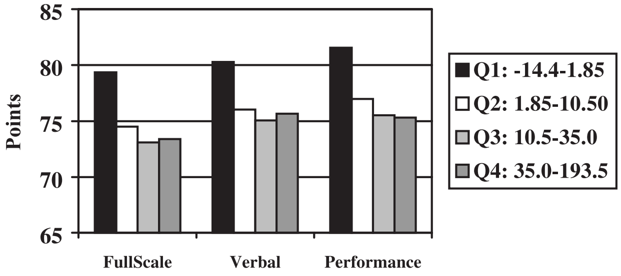

Figure 3b. Average BPb[2]

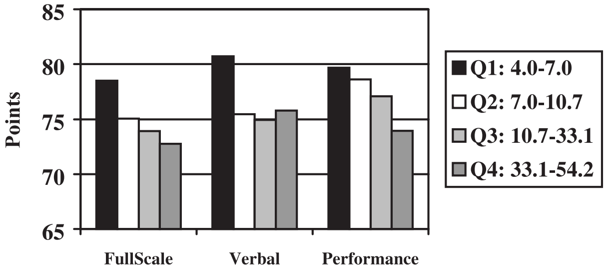

Figure 3c. Concurrent BPb

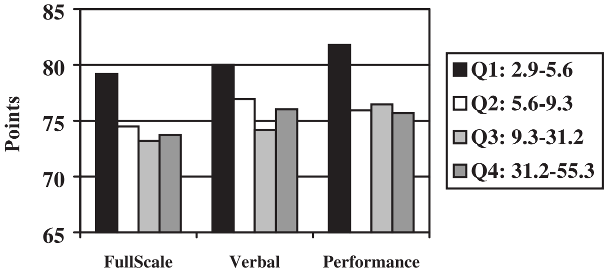

Fig. 3. Covariate-adjusted IQ means by quartiles of Tib-Pb and BPb[1].

[1] For 67% of the sample, quartile membership for Tib-Pb and BPb were identical.

[2] Quartile values are hypergeometric means.

bone and blood data ($N = 167$), we conducted covariate-adjusted analyses that examined associations with IQ/10–12 when Tib-Pb and two measures of BPb (CBPb and Avlog$_{10}$ BPb) were included in models, separately and together.

Table 4 presents the results of five analyses examining associations between BPb, Tib-Pb and IQ, after adjustment for the same socio-demographic covariates considered in Table 2, except for age (because Tib-Pb was measured at a single age). Although the magnitude of the associations between BPb and IQ are comparable to those shown in Table 2, the reduced sample size increases the standard error, thereby decreasing statistical significance.

Tib-Pb was a statistically significant predictor of Full Scale and Performance IQ, with or without CBPb or AvLog$_{10}$ BPb in the model. In contrast, once Tib-Pb was entered into the model, BPb was *not* a significant predictor of IQ, whether expressed as CBPb or AvLog$_{10}$ BPb. Although the use of different metrics makes it impossible to compare across measures of blood and bone lead, we calculated the number of IQ points that would be associated with doubling each of the exposure measures, controlling for the social factors noted in Table 2. For each doubling of Tib-Pb (from baseline Tib-Pb + 15), Full Scale, Performance, and Verbal IQ decrease by an estimated 2.41, 1.78, and 2.67 points, respectively. Comparable, though slightly smaller, deficits would be found with the doubling of the serial blood lead measure (the hypergeometric mean, or $10^{\mathrm{AvLog_{10}\,BPb}}$): 1.51, 1.27, and 1.54 points, respectively, lost from Full Scale, Performance, and Verbal IQ.

Because Tib-Pb and BPb are expressed in different metrics, numerical comparisons of the effect sizes (i.e., betas) cannot be interpreted. To permit comparisons, we classified children with Tib-Pb measurements into four groups of equal size, first by Tib-Pb and then by Avlog$_{10}$ BPb. Figure 3 presents the covariate adjusted means for Full Scale, Performance and Verbal IQ, by quartile of Tib-Pb (Fig. 3a) and, separately, by quartile of Avlog$_{10}$ BPb (Fig. 3b) and quartile of CBPb (Fig. 3c).

For lead measured in bone, the largest loss of IQ points appeared in the transition from Quartile 1 to Quartile 2. A similar pattern obtained when lead exposure was estimated using Avlog$_{10}$ BPb of CBPb (Fig. 3). These transitions correspond to Tib-Pb levels up to 1.85 µg Pb/g bone mineral, average serial BPb levels up to 7.00 µg/dl and concurrent BPb levels up to 5.6 µg/dl.

DISCUSSION

Our results extend previous findings (Wasserman et al., 1992, 1994, 1997, 2000) in this cohort of an adverse association between measures of BPb and childhood intelligence, after adjustment for a range of sociodemographic covariates. As in our earlier work, the contribution of BPb to intelligence was small relative to that of social factors. We also found significant associations between Tib-Pb and WISC-III Full-Scale, Performance and Verbal IQ. These latter associations persisted despite inclusion of BPb in the regression model. We infer, therefore, that associations between bone Pb and IQ outcomes are stronger than those between BPb measures and IQ.

BPb and Child Intelligence

Among the prospective studies of lead exposure, small deficits in both verbal and perceptual-motor aspects of intelligence, persisting through middle-late childhood, have been noted previously in the Boston and Port Pirie cohorts (Bellinger et al., 1992; Tong et al., 1996); these associations are similar in magnitude to those reported here. The persistence of such deficits is particularly troubling because the educational demands of the early teen years involve increasing demands on synthesis and abstraction in the processing and use of information. While consistent with other work, the clinical significance of such small associations is uncertain.

In previous analyses of IQ in the present sample, we found BPb associations consistently stronger for components of perceptual motor, rather than verbal, intelligence. At ages 10–12, however, BPb associations with both components of intelligence were similar. It is not clear whether the change in the specificity of the association with BPB reflects methodological or measurement differences (i.e., changes in the measure of cumulative BPb used, subtle changes in sample composition, or the application of the WISC-III to a non-English-speaking population), or whether it reflects a developmental change in the impact of chronic exposure. However, dose dependent decrements in Performance IQ appeared across the entire dose range, while decrements in Verbal IQ were confined to the transition between the lowest two quartiles of exposure.

The Measurement of Bone Lead in Children

This paper is the first to measure bone lead in a large sample of children with well-defined exposure histories using K-X-ray fluorescence, and to relate those measures to existing serial BPb assessments. Our instrumentation for measuring Tib-Pb was sufficiently sensitive to measure the tibia lead concentrations in most children. We found the expected associations between Tib-Pb and other variables; for example, Tib-Pb was higher among boys. Tib-Pb was also higher among children residing in Mitrovica, and within this group, higher among children living closer to the lead factory complex. Strong associations were found between Tib-Pb and BPb only among children in Mitrovica (i.e., those with relatively high and chronic exposure). In contrast, among those children with relatively low exposure, Tib-Pb and BPb were unrelated.

Tib-Pb, BPb and Intelligence

Associations between Tib-Pb and child intelligence persisted despite inclusion of BPb measures in the regression model. Across the entire range of exposure, Tib-Pb was associated with decreases in IQ; indeed, it appears from Figure 3 that these decreases are stronger among those at the lowest levels of exposure, with little further decrement in IQ at higher exposure levels. That the magnitudes of the associations between bone lead and IQ are more robust is not surprising in light of associations between bone lead and other health outcomes (Hu et al., 1994; Roels et al., 1994; Schwartz et al., 2000; Stewart et al., 1999).

Implications for Clinical Practice

Nearly all of the literature concerning the adverse impact of environmental Pb exposure on intelligence has used BPb as the marker of Pb exposure. Since the skeleton is the major repository for Pb exposure throughout life, and Tib-Pb is a better indicator of lifetime exposure, we wondered whether our previous evaluations of intelligence in this cohort might have underestimated the true associations between Pb exposure and IQ. In the subset of children with both bone and blood measures, Tib-Pb appears to be the more robust measure of exposure, by virtue of the fact that once it was added to our regression model predicting IQ, BPb became an insignificant predictor. However, based on our examination of quartiles of average and concurrent BPb and Tib-Pb (Fig. 3), either blood lead measure appears to provide a good estimate of the magnitude of associations with IQ. This correspondence suggests that the more readily obtained clinical measure, current blood lead, is a reasonable surrogate for more labor-intensive measures (i.e., bone or lifetime blood lead).

Despite the greater magnitude of association between Tib-Pb and IQ, we conclude that, for children with chronic exposures, current BPb measurements also provide a useful means for assessing the associations between Pb exposure and IQ. This is reassuring in that most clinicians are unable to assess bone lead in a standardized fashion, and since its assessment places substantial demands in terms of instrumentation cost and assessment time. In view of the far greater inconvenience, to both children and clinicians, to obtain measures of Tib-Pb, we recommend that the Centers for Disease Control and Prevention should continue to derive its ‘‘action levels’’ based on BPb, not bone lead.

A striking finding of these analyses, consistent with the work of others, is that the greatest decrements in intelligence appear to occur in the relatively low range of Pb exposure. This is consistent with the often-documented decrease in IQ as a function of the *log* of BPb concentration. The implications of this finding are that the current CDC ‘‘action level’’ for BPb of 10 μg/dl may be too high to afford protection against the small adverse effects of Pb on intelligence. If an ongoing combined data analysis from several prospective studies, including this one (Lanphear, 2000), reaches the same conclusion, the CDC may need to once again readdress the BPb standard in children.

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