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Association of Cumulative Lead and Neurocognitive Function in an Occupational Cohort

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Lead is a neurotoxicant that accumulates in bone with a half life of 25–30 years. To evaluate the association of lead biomarkers and cognitive function, a cohort of exposed and nonexposed workers who had been previously assessed in 1982 was retested approximately 22 years later. For the current assessment, both blood lead and tibia bone lead levels were determined. In addition, cognitive function was tested with the Pittsburgh Occupational Exposures Test battery, which had previously been administered in 1982. In exposed workers, bone lead level predicted lower current cognitive performance and cognitive decline over 22 years. In those lead-exposed workers older than age 55, higher levels of bone lead predicted poorer cognitive scores, suggesting vulnerability for older workers with higher past lead exposure. Finally, there was no association with bone lead level and recency of exposure, suggesting that cumulative body burden is most likely responsible for the progressive cognitive decrement evidenced with vulnerability because of aging.

Keywords: occupational, lead, cognitive, longitudinal, neuropsychology

In adults, occupational lead exposure is associated with cognitive deficits in tests of psychomotor speed, manual dexterity, and learning and memory ability (Stewart & Schwartz, 2007). Whether cumulative occupational exposure to lead causes progressive decrements in specific cognitive domains, and whether this effect is modified with aging, has been of recent concern (Weisskopf & Myers, 2006).

The skeleton is the major repository for lead within the body, sequestering up to 95% of lead with a half life of 25–30 years (Aro, Todd, Amarasiriwardena, & Hu, 1994; Brito et al., 2002; Hu, Aro, & Rotnitzky, 1995; Hu, Milder, & Burger, 1990, 1991; Hu, Pepper, & Goldman, 1991). Lead may be mobilized into circulation from skeletal stores when there is high bone turnover, such as in age-related osteoporosis (Todd & Chettle, 1994). The most reliable biomarkers that estimate content of lead in the body are blood and bone lead levels. Bone lead level reflects cumulative dose (Dorsey et al., 2006; Ganellin et al., 2000; Lee et al., 2000). Blood lead level is presumed to reflect exposure received in the most recent few months, but it is actually a composite index that reflects the equilibrium between ongoing exposure, excretory loss, and movement of lead from bone (Brito, McNeill, Webber, & Chettle, 2005; Brito et al., 2002).

An underlying concern with occupational lead exposure is whether its cumulative effect will alter age-related changes in the nervous system. Increasing age is associated with diminished neuropsychological performance and reserve capacity in the nervous system (Bleecker, Lindgren, & Ford, 1997). The increased susceptibility of the older nervous system to lead neurotoxicity has not been adequately addressed in the literature.

Lead may impair cognition both as an acute effect of recent dose and a chronic effect of cumulative dose. In a study of South Korean workers with ongoing lead exposure (Schwartz et al., 2005), significant inverse associations of current blood lead level with executive ability and manual dexterity were reported, and tibia lead level predicted longitudinal changes in the same domains.

In a recent review, 15 studies of current or past occupational lead exposure and cognitive effects were analyzed (Shih, Hu, Weisskopf, & Schwartz, 2007). Eight of these studies used a surrogate measure of cumulative lead dose, integrated blood level. Cognitive changes were compared for current blood lead level and integrated blood level dose. An inverse association was reported between blood lead level and cognitive function when exposure was primarily current. However, in studies in which the exposure was primarily in the past (integrated blood level), the cumulative dose measure was a more significant predictor of worse cognitive function than was blood lead level.

Years after occupational exposure is stopped, lead may continue to cause progressive cognitive deficits (Links, Schwartz, Simon, Bandeen-Roche, & Stewart, 2001). Tibia lead level has been shown to be related to lower cognitive scores in a cross-sectional analysis of 535 former lead workers whose last exposure was, on average, 16 years earlier (Schwartz et al., 2000; Stewart et al., 1999). Longitudinal analysis of the same cohort found that tibia

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lead level also predicted cognitive declines over time (Schwartz et al., 2000). No association was noted with current blood lead level and cognitive test results.

To determine whether long-term occupational exposure to lead in adults can cause progressive changes in cognitive function with aging, we conducted a follow-up of 83 lead-exposed and 51 nonexposed workers in 2004. We report the results of this follow-up evaluation of workers initially tested in 1982. We hypothesized that workers with higher lead biomarkers would have a greater risk of overall cognitive decline, and in specific cognitive domains with aging, compared with nonexposed workers. To our knowledge, this is the longest follow-up on the same cohort to date, using the same test battery.

Method

Study Population

The Lead Occupational Study was a cross-sectional evaluation conducted in 1982 with 288 lead-exposed and 181 nonexposed male workers (Parkinson, Ryan, Bromet, & Connell, 1986). Exposed workers were drawn from company lists at three lead battery plants located in eastern Pennsylvania. Unexposed control workers were enrolled from a neighboring location that manufactured truck chassis and had no documented exposure to lead or other neurotoxic chemicals. Inclusion criteria for the initial evaluation were that a participant had to have been employed for at least 1 year and be an English-speaking Caucasian male between the ages of 18 and 60.

The 1982 Lead Occupational Study compared cognitive function in lead-exposed and nonexposed workers using the Pittsburgh Occupational Exposures Test (POET) battery (Parkinson et al., 1986). Factor analysis of the POET battery with the original nonexposed control participants revealed five primary cognitive domains: psychomotor speed, spatial function, executive function, general intelligence, and learning and memory (Parkinson et al., 1986; Ryan, Morrow, Bromet, & Parkinson, 1987; Ryan, Morrow, Parkinson, & Bromet, 1987).

There were no differences between the groups in age or education at the initial testing at Visit 1 in 1982. The mean blood lead level as reported in two published articles was 40 μg/dl in lead-exposed workers and 7.2 μg/dl in nonexposed workers (Parkinson et al., 1986; Ryan, Morrow, Parkinson, & Bromet, 1987). Only blood lead level was measured at Visit 1. As mentioned in these articles, after controlling for age, education, and income, lead-exposed workers scored significantly lower on tests of psychomotor speed, with the differences limited to older workers. Because the original data were collected on older mainframe computers that became obsolete over time, it was not possible to retrieve original identities to link them to the earlier records regarding income, alcohol use, and blood lead level. The original cognitive test scores were still accessible from a printout and were available for this analysis. Because of the deidentification of the data, no direct comparison can be done between the lead-exposed and nonexposed groups tested at Visit 1 and those who returned for the reevaluation in 2001–2004 (Visit 2). However, we found significant differences on only two tests when we compared cognitive scores for men who returned for Visit 2 with those for men who did not return. Those who returned had slightly faster reaction times with their dominant hand on the Grooved Pegboard Test ($p < .001$) and slightly better recall on the total learning trials of the Verbal Paired Associate Learning Test ($p < .041$). This suggests that workers who came back at Visit 2 may have had somewhat better cognition, negating the possibility that only those participants with poorer cognitive function volunteered for the follow-up assessment. Those who returned also were also slightly more educated (11.6 years vs. 11.2 years, $p < .032$).

The current study presents results for 83 of the original lead-exposed workers (29% of the original workers exposed at Visit 1) and 51 of the nonexposed workers (28% of the original nonexposed workers at Visit 1). At Visit 2, current lead levels in blood and bone were measured. The study protocol was approved by institutional review board of the University of Pittsburgh, and all participants provided written informed consent. The University of Pittsburgh Radiation Safety Committee approved the x-ray fluorescence (K-XRF) protocol.

Data Collection

Data were collected at the University of Pittsburgh. All participants completed baseline testing in a standard order: standardized questionnaire to assess demographic and background information, blood pressure, height, weight, cognitive testing, and lead measurements. Tests were administered by a research technician trained in the reliable administration of neuropsychological tests and supervised by Lisa A. Morrow.

Cognitive test battery. The POET Battery (Ryan, Morrow, Bromet, & Parkinson, 1987) is outlined in Table 1.

Biologic Measurements

Bone lead levels. Bone lead concentration was obtained in tibia, using the K-XRF technique (Chettle, 2005). The K-XRF uses 88.025 keVs from ^{109}Cd induced lead K-shell x-ray fluorescence, measured with a backscatter counting geometry. A 30-min measurement was taken at the midshaft of the left tibia after washing with a 50% solution of isopropyl alcohol. The tibial midshaft was taken as the midpoint between the tibial plateau and the medial malleolus. The K-XRF beam collimator was sited perpendicularly to the flat bony surface of the tibia. Tibia lead level was expressed in units of micrograms lead per gram of bone mineral (hereinafter referred to as μg/g). To maintain quality control, a check standard (Lucite-encased lead target) was run before participant measurement. As done previously (Stewart et al., 1999), because of variability in the time since last occupational exposure to lead, we used years since last exposure to estimate tibial lead levels at the termination of lead exposure, referred to as *peak tibia lead* (Gerhardsson et al., 1993). Current tibia lead levels were extrapolated back using clearance half-time of tibia lead of 27 years, assuming first-order (mono-exponential) clearance from tibia, with $k = (0.693/t_{[1/2]})$, $t_{[1/2]} = 27$ years, and $t =$ years since last exposed to lead. Peak tibia lead = [(current tibia lead) $\times$ $e^{(k \times t)}$]. As recommended in other epidemiologic studies, we retained all bone lead level values, including those below zero (Hu, Shih, Rothenberg, & Schwartz, 2007).

Blood lead levels. A 5.0-ml blood sample for lead measurement was taken by venipuncture in a special lead-free tube containing ethylene-diamine-tetra-acetic acid. Lead level was determined using atomic absorption spectrophotometry conducted by

Table 1
Pittsburgh Occupational Exposures Test Battery

Measure	Description
	Factor 1: Learning and Memory
Verbal Paired Associative Learning	Each of 10 pairs of unrelated nouns was read to the participant while presented visually over four trials. Participants were tested by presenting the first word of each pair as a retrieval cue.
Delayed verbal recall	Each of the 10 word pairs was assessed 30 min later by cuing participants with the first word of each pair.
Symbol–digit paired associate learning	Seven symbols, each paired with a single digit, were presented one at a time for 3 s, and after each presentation trial, participants were asked to recall the number paired with the symbol. Four trials were administered.
Delayed symbol recall	Recall of the symbol–digit pairs was assessed 30 min later.
Incidental recall	Recall of the symbols from the revised Wechsler Adult Intelligence Scale (WAIS–R) Digit Symbol Substitution Test (Wechsler, 1981) was queried.
Recurring words Test	Participants were presented with a series of four-letter words and asked to recall which ones were previously presented.
	Factor 2: Spatial Function
Visual reproductions	This subtest from the Wechsler Memory Scale (Wechsler, 1945) was administered in the standard fashion.
Visual reproductions delayed recall	Recall of the designs was assessed 30 min later.
Embedded Figures Score	Simple line drawings were shown along with four complex patterns, and participants were asked to identify the matching design (Ryan & Butters, 1980).
Block design subtest	This WAIS–R subtest was administered in the usual manner. (Wechsler, 1981).
	Factor 3: Psychomotor Speed
Part A of the Trail Making Test	This test was administered in standard fashion.
Embedded Figures Time	Mean time to find correct solutions (Ryan & Butters, 1980; see above).
Grooved Pegboard	Time to insert 25 pegs in a pegboard (first with dominant hand and then with nondominant hand; Lafayette, 1987).
	Factor 4: Executive Function
Part B of the Trail Making Test	This test was administered in the standard fashion.
Digit Span and Digit Symbol	These WAIS–R subtests were administered in the usual manner.
	Factor 5: General Intelligence
WAIS–R Information, Picture Completion, and Similarities	These tests were administered in the standard fashion.

the Central Laboratory Service Inc., an affiliate of the University of Pittsburgh Medical Center. The lab is certified for the analysis of lead in blood by the Occupational Safety and Health Administration and the Centers for Disease Control and Prevention. The lowest detectable level reported by the lab during this study was 3 μg/dl.

Covariates. Information regarding age, cigarette smoking history (current or never), family income (>40,000 or ≤40,000 per year), education (years), and alcohol use (drinks per week) was obtained from the interview. Systolic and diastolic blood pressure in mmHg was measured. Body mass index was calculated as the weight in kilograms divided by the square of height in meters. The numbers of years of employment and time since last worked, with and without lead, were ascertained.

Statistical Analyses

Baseline characteristics by exposure status were compared by means of chi-square tests for categorical variables and either two-sample *t* test or Wilcoxon's Mann–Whitney *U* test for continuous variables. Interquartile ranges were the difference between values at the 75th and 25th percentile levels of a given distribution for non-normal variables (bone lead level, blood lead level, years since last worked with lead, and drinks/week). Two-tailed *p* values were used for all tests, at 5% statistical significance. Participants were analyzed by exposure status, that is, exposed ($n = 83$) and nonexposed ($n = 51$). We further divided the workers into two age groups, dichotomized at age 55 years for stratified analysis because the current neuropsychology literature reports this age cutoff for comparison of cognitive changes with aging (Denburg, Tranel, & Bechara, 2005; Fein, McGillivray, & Finn, 2007). These categories were exposed, younger than age 55 ($n = 54$), exposed age 55 or older ($n = 29$), nonexposed younger than age 55 ($n = 23$), nonexposed age 55 or older ($n = 28$). The POET battery was summarized into five cognitive domains to minimize multiple comparisons. Cognitive tests for each of the five domains were *z* transformed and standardized for direction so that a negative regression coefficient indicated worse performance with increasing lead. In addition, a total cognitive score was obtained by averaging all five *z* scores.

We used linear regression analysis to determine the association of cognitive function with lead biomarkers, cross sectionally at Visit 2 and longitudinally from Visit 1 to Visit 2. To determine cross-sectional association of lead biomarkers with cognition at Visit 2, we used regression analysis stratified by exposure. The exposed group was stratified further by age into younger than 55 and 55 or older. To predict cognitive change over time, from Visit 1 to Visit 2 we used regression analysis stratified only by exposure.

We ran separate models for each cognitive domain with sequential adjustment for peak tibia lead level, blood lead level, both together, and both lead biomarkers together with lead employment variables. For longitudinal analysis, we created a new change variable as a Visit 2 − Visit 2 − Visit 1 score for all the domains and the total score. In this analysis, we controlled for baseline score at Visit 1 in addition to the covariates. We only used tibia lead scores for longitudinal analysis. We did not analyze blood lead levels in the change models because these were not available from the Visit 1 testing. A Huber White Sandwich estimator of variance was used with robust regression to construct valid standard errors.

In multivariate models, we included variables that were significantly associated with cognition or lead exposure either reported in the literature or from preliminary univariate analysis (age and education). To assess potential interactions between lead and other covariates, we created multiplicative interaction terms between the lead and other covariate variables and included them in the model along with the main effects. All linear regression models were evaluated for outliers; examination of added variable plots and partial residual plots suggested five influential points that were removed from analysis.

To assess the magnitude of difference in effect of peak tibia lead level on the cognitive score, we calculated the effect size: *d* as defined by Cohen (Cohen, 1988). This *d* is the difference between the means, $M_{\text{Exposed}} - M_{\text{Nonexposed}}$, divided by pooled standard deviation of the two groups. We also used the "listcoef" function of STATA (edition 9, StataCorp, College Station, TX) to distinguish the effect of 1 standard deviation increase in peak tibia lead on 1 standard deviation change in cognitive score and compared it with 1 standard deviation increase in age.

Results

Table 2 presents demographic data for the two groups. The lead-exposed workers were slightly younger in age and less educated than the nonexposed workers. The median peak tibia lead level was 57 μg/g in lead-exposed workers and 12 μg/g in nonexposed workers ($p < .001$). The median blood lead level was 12 μg/dl in lead-exposed workers and 3 μg/dl in nonexposed workers ($p < .001$). Body mass index, income, smoking, drinking, blood pressure were comparable in the two groups. Bone lead levels were correlated with systolic blood pressure in exposed workers ($r = .28$, $p < .05$).

Cross-Sectional Analysis by Exposure Status

Table 3 presents unadjusted mean cognitive scores (presented as *z*-score transformations) for lead exposed and nonexposed workers at Visit 1 and Visit 2. At Visit 2, mean total cognitive score and spatial function and general intelligence scores were significantly lower in lead-exposed as compared with nonexposed workers ($p < .001$). Table 4 presents model specifications for overall cognitive score and bone lead levels for covariates at Visit 2. Peak tibia lead level was a significant predictor of overall cognitive function in the lead-exposed group, but not in the nonexposed group. In nonexposed workers, age and education were the only significant predictors. Spearman correlations for the lead biomarkers, age, and cognitive scores are given in Table 5. In lead-exposed workers, after partialing out the effect of age, there was a significant inverse association of all scores with peak tibia lead level except the motor domain.

Regression analyses were run predicting overall cognitive score, adjusted for all the covariates considered and for lead biomarkers (blood and bone). Covariate adjusted models were also run for all cognitive domains (see Table 6). Beta coefficients were consistently negative in lead-exposed workers, and higher peak tibia lead level was associated with lower scores for the overall cognitive domain ($p < .01$; see Figure 1) and for general intelligence ($p < .05$), learning and memory, and the spatial domain (all *p*s $< .05$). Blood lead level was not associated with any of the cognitive scores. When both blood and peak tibia lead levels were analyzed together, bone lead level predicted a significant inverse association in three of the five domains.

Table 2
Demographic Characteristics in Lead-Exposed and Nonexposed Male Workers in 2004

Characteristic	Nonexposed ($n = 51$)	Exposed ($n = 83$)	*p*
Age (years; *M*[*SD*])	55 (9)	54 (9)	.458
Body mass index (kg/m^2; *M*[*SD*])	31 (6)	30.6 (6)	.739
Systolic blood pressure (mmHg)	131 (2.5)	127 (1.8)	.191
Diastolic blood pressure (mmHg)	78 (1.3)	78 (1)	.848
Education (years; *M*[*SD*])	12.2 (1.8)	11.34 (1.7)	.005
Income (*n* [%])			
>$40,000	28 (54)	51 (57)	.690
≤$40,000	24 (46)	38 (43)	
Smoker (*n* [%])	10 (19)	23 (26)	.371
Drinks (per week; *Mdn* [Iqr])	2 (0, 3)	1 (0, 4)	.342[a]
Blood lead level (μg/dl; *Mdn* [Iqr])	3 (3, 4)	12 (8, 19)	<.001[a]
Bone lead level (μg/g bone mineral; *Mdn* [Iqr])	12 (−8, 32)	57 (20, 86)	<.001[a]
Employment (years; *M*[*SD*])	27 (7)	25 (8)	.134
Employment with lead (years; *M*[*SD*])	—	25 (8)	—
Last work (years; *M*[*SD*])	0.04 (0.3)	0.33 (0.3)	.007
Last worked with lead (years; *Mdn* [Iqr])	—	6 (0.02, 16)	—

Note. $N = 134$. Iqr = Interquartile range.
[a]Nonparametric Wilcoxon, Mann-Whitney *U* test.

Table 3
Unadjusted Mean z Scores in 1982 and 2004 in Lead-Exposed and Nonexposed Male Workers

	1982			2004		
Cognitive domain	Nonexposed (n = 51; M[SD])	Exposed (n = 83; M[SD])	p	Nonexposed (n = 51; M[SD])	Exposed (n = 83; M[SD])	p
Total score	0.00 (2)	−1.09 (3)	.012	−0.00 (2)	−1.35 (3)	.008
Motor	0.00 (3)	−1.21 (3)	.031	−0.00 (3)	−1.27 (5)	.105
Spatial	0.00 (3)	−1.53 (4)	.013	0.00 (3)	−1.88 (4)	.003
Executive	0.00 (2)	−0.26 (3)	.545	−0.00 (2)	−0.63 (3)	.139
General intelligence	0.00 (2)	−1.24 (2)	.003	0.00 (3)	−1.54 (3)	.001
Memory	0.03 (4)	−1.25 (6)	.153	−0.00 (5)	−1.43 (6)	.119

Age-Stratified Cross-Sectional Analysis for Lead-Exposed Workers (Visit 2)

Table 7 presents results for lead-exposed workers when further stratified by age. In workers age 55 or older, higher peak tibia lead level was associated with lower scores for total cognitive score ($p < .05$), spatial function ($p < .01$), learning and memory ($p < .01$), and general intelligence ($p < .01$; see Figure 2). There were no associations in the younger lead-exposed group or in either of the two nonexposed age groups.

Longitudinal Analysis by Exposure Status

In lead-exposed workers, peak tibia lead level predicted cognitive decline from Visit 1 to Visit 2 for total cognitive score, spatial ability ($p < .01$ for both), and executive function ($p < .05$; see Table 8). No such association was observed in the nonexposed workers.

On the basis of recent findings in the literature (cf. Schwartz et al., 2000), we hypothesized that cumulative lead dose, as measured in bone, was instrumental in progressive cognitive decrements. However, a portion of the lead-exposed sample (n = 32, or 39%) had worked with lead within the past several months before their follow-up assessment. To determine whether recency of exposure influenced outcome, we ran correlations between recency (interquartile range = 0.02 years to 16 years) and both total cognitive score and peak tibia lead level. Correlations were low and nonsignificant ($r < .17$). Peak tibia lead levels were also higher for persons who had not worked with lead for more than a year compared with those who had more recent exposure (80 μg/g vs. 62 μg/g, respectively). In regression models, peak tibia lead level was associated with significantly lower total cognitive scores only in those who had not been exposed for more than a year ($p = .008$). When we repeated the same models after further categorizing these workers into age 55 or older and younger than age 55, we observed significant association only in workers who were age 55 or older and had worked with lead more than a year ago ($p < .011$). These findings support the premise that cumulative body burden, not recency of exposure, is most likely responsible for the progressive cognitive decrement evidenced with vulnerability because of aging.

Table 4
Regression Coefficients and Model Specification for Overall Cognition and Bone Lead Levels in Lead-Exposed and Nonexposed Male Workers in 2004 at Visit 2

Covariates	Exposed (n = 83)		Nonexposed (n = 51)	
	β	p	β	p
Peak tibia lead level (ug/g)	−0.282	.01	−0.001	.91
Blood lead level (ug/dl)	−0.079	.44	−0.228	.11
Age (years)	−0.510	.01	−0.228	.11
Education (years)	0.184	.04	0.523	.01
Income ($)	0.185	.06	0.256	.02
Blood pressure (mmHg)	−0.006	.94	0.088	.41
Smoking (no. cigarettes)	0.043	.62	0.059	.47
Drinking (drinks/week)	0.095	.24	−0.174	.04
Years worked with lead	0.208	.15	—	—
Years since worked with lead	−0.006	.94	—	—
Model R^2	0.59		0.61	
F	(10, 72)		(8, 42)	
Prob > F	0.001		0.001	

Effect Size

The effect size in the mean total cognitive score of the lead-exposed and nonexposed workers at Visit 2 was 0.49 and at Visit 1 was 0.45—a moderate effect size (Cohen, 1988). The magnitude of difference in cognitive change with lead at Visit 2 was assessed as the effect of 1 standard deviation decrease in total cognitive score per 1 standard deviation increase in peak tibia lead level. The effect of lead was 48% of 1 standard deviation increase in age in years in lead-exposed workers. In the nonexposed group, 1 standard deviation increase in bone lead level only caused 35% decrease in total cognitive score observed per standard deviation increase in age. The lead-exposed workers experienced 17% greater loss in total cognitive score as compared with nonexposed workers.

Discussion

In this follow-up evaluation of occupational lead exposure, we found that peak tibia lead level, a marker of cumulative exposure, significantly predicted lower cognitive scores in lead-exposed workers—both cross-sectionally and longitudinally. The most consistent association was between peak tibia lead level and spatial ability, learning and memory, and total overall cognitive score. When exposure was assessed by age, this association was more significant in older lead-exposed men (split at age 55). That is, older lead-exposed workers had beta coefficients almost five times

Table 5
Spearman Correlations for Cognitive Scores With Lead Biomarkers and Age in Lead-Exposed and Nonexposed Male Workers in 2004 at Visit 2

	Exposed				Nonexposed			
Cognitive domain	Age	Blood lead level	PTL	PTL, age partialed out	Age	Blood lead level	PTL	PTL, age partialed out
Total score	−0.52**	*ns*	−0.38**	−0.23*	−0.50**	*ns*	*ns*	*ns*
Motor	−0.57**	*ns*	−0.23*	0.06	−0.63**	−0.29*	*ns*	*ns*
Spatial	−0.47**	*ns*	−0.35**	−0.25*	−0.41**	*ns*	*ns*	*ns*
Executive	*ns*	*ns*	−0.32*	−0.21*	*ns*	*ns*	*ns*	*ns*
General intelligence	*ns*	*ns*	−0.32**	−0.26*	*ns*	−0.30*	*ns*	*ns*
Memory	−0.51**	*ns*	−0.39**	−0.26*	−0.50**	−0.31*	*ns*	*ns*

Note. PTL = peak tibia lead level.
* $p < .05$. ** $p < .01$.

lower than those of younger lead-exposed workers for the three cognitive domains. This association was seen even after controlling for current blood lead levels.

These results are consistent with recent research that has reported that past lead exposure is particularly detrimental to the aging brain and that specific cognitive domains may be particularly vulnerable. That is, Stewart et al. (2006) found a significant inverse association of peak tibia lead level with scores on executive ability, learning and memory, and manual dexterity in men with past occupational exposure to lead. In a subsequent study using MRI with the same cohort, peak tibia lead level predicted significant association with lower brain volume in frontal and total gray matter and parietal white matter (Stewart et al., 2006). Stewart et al. suggested that long-term past lead exposure (i.e., decades earlier) was progressive over time and resulted in these structural brain lesions (Schwartz et al., 2005; Schwartz & Stewart, 2007; Shih et al., 2007).

The toxic mechanisms underlying the effects of lead on the central nervous system have been of more recent interest (Dorsey et al., 2006; Nilson, Sallsten, Hagberg, Backman, & Barregard, 2002; Schwartz et al., 2005). Lead alters the permeability of the blood–brain barrier (Struzynska, Walski, Gadamski, Dabrowska-Bouta, & Rafalowska, 1997) and accumulates in astroglia, which are essential for maintenance of neuronal environment. Lead exposure is now thought to interfere with several calcium-dependent processes and activate protein kinase C, which has been implicated in neurotoxicity (Hwang et al., 2002). There is experimental evidence that lead can cause white matter damage, cell death, and changes to cellular architecture. Lead has also been reported to affect specific areas in the brain such as the hippocampus and frontal cortex (Chang, Chen, Wei, & Chen, 2006; Heidmets, Zharkovsky, Jurgenson, Jaako-Movits, & Zharkovsky, 2006; Li, Liu, Liu, Ge, & Zou, 2006; Mandelbaum, 2006).

One of the distinguishing features of this study was the comparison of lead-exposed and nonexposed workers over a time span

Table 6
Multiple Regression Models With Standardized Beta Coefficients for Cognitive Scores for Lead-Exposed and Nonexposed Male Workers in 2004 at Visit 2

	Total score		Motor		Spatial		Executive		General intelligence		Memory	
Lead measures	Exposed	Nonexposed	Exposed	Nonexposed	Exposed	Nonexposed	Exposed	Nonexposed	Exposed	Nonexposed	Exposed	Nonexposed
Tibia lead level[a]	−0.265**	0.044	−0.015	−0.049	−0.282*	−0.055	−0.215	0.221	−0.219	0.024	−0.262*	0.063
Blood lead level[b]	−0.075	−0.254	−0.057	−0.338	−0.040	0.089	−0.153	−0.270	0.057	−0.195	−0.078	−0.273
Tibia lead level	−0.260**	0.029	−0.002	−0.069	−0.289*	−0.050	−0.182	0.206*	−0.251*	0.013	−0.256*	−0.049
Blood lead level[c]	−0.019	0.252	−0.057	−0.342	−0.023	−0.086	−0.113	−0.257	−0.112	−0.23	−0.022	−0.234*
Tibia lead level	−0.284**	−0.011	−0.052	−0.041	−0.312**	−0.096	−0.192	0.156	−0.259*	−0.013	−0.256*	−0.004
Blood lead level[d]	−0.079	−0.228	−0.094	−0.345	−0.037	−0.107	−0.113	−0.219	−0.305**	−0.167	−0.161	−0.205

Note. Lead-exposed workers, $N = 53$; nonexposed workers, $N = 51$. All models adjusted for age and education.
[a] Model 1 adjusted in addition for peak tibia lead level in ug/g of bone. [b] Model 2 adjusted also for blood lead level in ug/dl. [c] Model 3 adjusted for peak tibia lead and blood lead levels together. [d] Model 4 adjusted for peak tibia lead level, blood lead level, years of employment with lead, and years since last work with lead, income, drinks/week, smoking, and blood pressure.
* $p < .05$. ** $p < .01$.

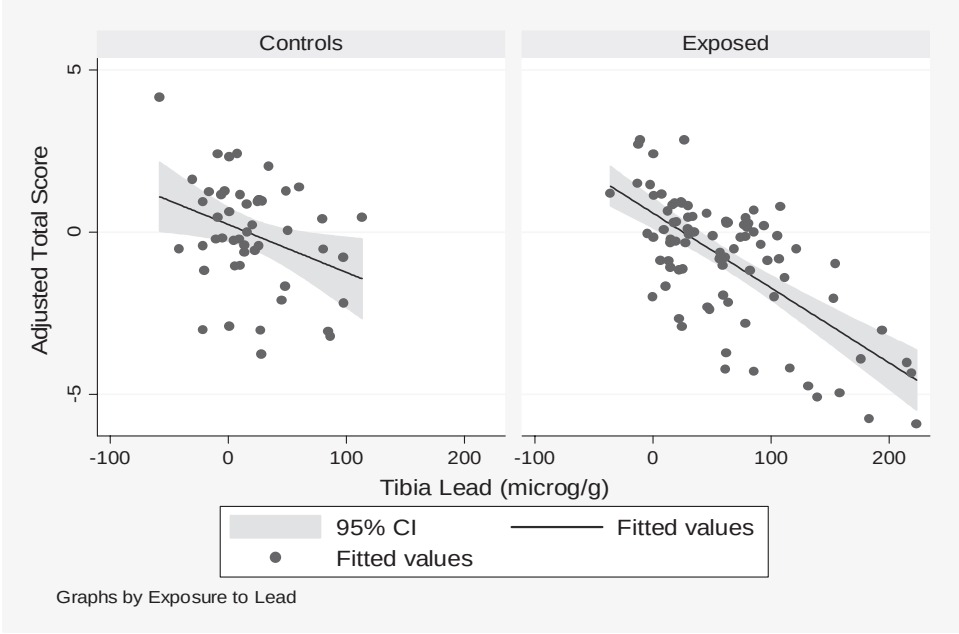

Figure 1. Adjusted total *z* score and bone lead levels in exposed and nonexposed (control) male lead workers in 2004.

of 22 years. For lead-exposed workers, significant declines in performance in the spatial and executive domains, and the overall total score, were predicted by tibia lead levels, even after controlling for baseline scores, age, education, years of employment, and lifestyle factors. No association was noted in the nonexposed workers after controlling for the covariates. To our knowledge, this is the first study to explore the association of bone lead levels with the longest follow-up time on the same occupational cohort. These results are similar to those of several other reported studies in recent literature. In a longitudinal study of 576 current and former lead workers in South Korea, three study visits occurred during a mean follow-up duration of 2.2 years (Schwartz et al., 2005). There were consistent associations of blood lead level with test scores at baseline and of tibia lead level with declines in test scores over the follow-up, mainly in executive abilities, manual dexterity, and peripheral vibration threshold. Similarly, in another study of 535 former lead workers (none of whom had been exposed for an average of 16 years) in the United States, neurobehavioral and lead measures were assessed two to four times over 4 years (Schwartz et al., 2000). Peak tibia lead level predicted decline over the 4-year testing interval for tests of verbal learning and memory, visual memory, executive ability, and manual dexterity. Taken together, our results and those of Schwartz et al. (2005) support the inference that past history of occupational lead exposure may lead to longer term (possibly progressive) effects on cognitive decline as a function of cumulative dose. Moreover, there was no association with bone lead and recency of exposure, suggesting that cumulative body burden is most likely responsible for the progressive cognitive decrement evidenced with vulnerability because of aging.

Lead exposure is also a risk factor for hypertension, which may cause cerebrovascular disease leading to poor performance on cognitive tests (Glenn et al., 2006; Glenn, Stewart, Links, Todd, & Schwartz, 2003; Nawrot, Thijs, Den Hond, Roels, & Staessen, 2002). Increase in blood pressure may be an intermediate variable on the hypothesized causal path between lead exposure and cognitive changes. Lead and homocysteine are both associated with cardiovascular disease and cognitive dysfunction (Schafer, Glass, Bolla, et al., 2005). An association between blood lead level and

Table 7
Multiple Regression Models for Cross-Sectional Cognitive Scores in 2004 in Lead-Exposed and Nonexposed Male Workers, Stratified by Age and Exposure

	Total score		Motor		Spatial		Executive		General intelligence		Memory	
Cognitive domain	Exposed	Nonexposed	Exposed	Nonexposed	Exposed	Nonexposed	Exposed	Nonexposed	Exposed	Nonexposed	Exposed	Nonexposed
≥age 55	−0.523*	−0.102	−0.224	−0.315*	−0.628**	−0.126	−0.212	0.099	−0.306**	0.144	−0.525*	−0.095
<age 55	−0.137	−0.084	−0.092	0.174	−0.111	−0.294	0.048	0.141	−0.108	−0.113	−0.125	−0.059

Note. Adjusted for education, income, years of employment, years since last worked, smoking, drinks/week, and blood pressure.
* $p < .05$. ** $p < .01$.

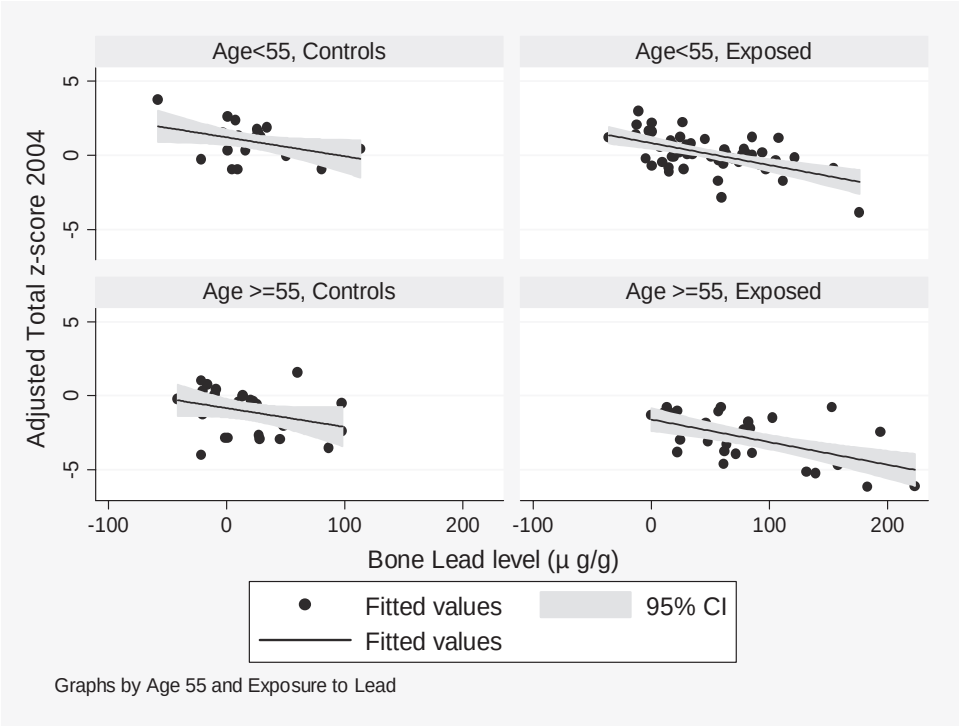

Figure 2. Adjusted total *z* scores and bone lead levels in exposed and nonexposed (control) male lead workers by age.

homocysteine has also been documented (Schafer, Glass, Bressler, Todd, & Schwartz, 2005), which could be a common mechanism that explains the effects of lead on the cardiovascular and nervous systems. However, even after controlling for hypertension in the current analysis, the effects remained significant.

The most consistent association between lead and lower cognitive function was noted for the spatial domain. Similar associations between lead and spatial function were reported in the Normative Aging Study, which looked at environmental lead level levels in a cohort of older men both cross sectionally (Payton, Riggs, Spiro, Weiss, & Hu, 1998) and longitudinally (Weisskopf et al., 2004). Childhood lead exposure has also been associated with decrement in spatial copying and spatial memory ("Air Quality Criteria for Lead," 2006).

There are a number of strengths to our study. We studied a well-characterized cohort of lead-exposed and nonexposed workers, using state-of-the-art measurements of K-XRF and controlling for a number of important covariates. In addition, we assessed workers at the initial and follow-up testing with the same battery of cognitive tests. However, there may be some recall bias in this study. Initial studies from the 1981–1984 sample reported no significant difference, except psychomotor speed, between the lead-exposed and nonexposed workers (Parkinson et al., 1986; Ryan, Morrow, Parkinson, & Bromet, 1987). For the current analysis, when we compared the Visit 1 unadjusted mean scores between lead-exposed and nonexposed workers for the current cohort, there were significant differences between spatial and general intelligence function, in addition to psychomotor scores. This difference may be because the workers who came back for Visit 2 may have been those who performed at the lowest range of cognition at the initial evaluation. However, this is somewhat negated by the fact that when we compared Visit 1 scores for those

Table 8
Multiple Regression Models for Cognitive Change From 1982 (Visit 1) to 2004 (Visit 2) in Lead-Exposed and Nonexposed Male Workers

Peak tibia lead level (ug/g)	Total score	Motor	Spatial	Executive	General intelligence	Memory
Exposed	−0.352*	−0.095	−0.338*	−0.342*	−0.188	−0.130
Nonexposed	0.049	−0.030	−0.079	0.166	−0.048	0.137

Note. Adjusted for age, education, income, blood pressure, years of employment, years since last worked, smoking, drinks/wk, and baseline scores.
* $p < .01$.

who did and did not return for the follow-up testing, we found that those who did not come back were less educated and scored more poorly on verbal memory tests. Thus, it does not support a hypothesis that only those with lower cognition retuned for the follow-up testing.

A national public health objective for 2010 is to reduce the blood lead levels greater than 25 μg/dL among the workforce to zero ("Adult Blood Lead Epidemiology and Surveillance–United States, 2003-2004," 2006). The Occupational Safety and Health Administration requires workers to have an annual medical evaluation if blood lead levels exceed 40 μg/dL and to be removed from the workplace if levels exceed 50 μg/dL (Lead, 29 C.F.R. 1910.1025). Projections using 2003–2004 Adult Blood Lead Epidemiology and Surveillance data trends indicate that the national prevalence rate of adults with blood lead levels greater than or equal to 25 μg/dL will be approximately 5.7 per 100,000 employed adults in 2010. Increased prevention measures in work environments will be necessary to reduce this rate to zero and decrease risk of cognitive decline in the workforce.

In summary, our data suggest that higher tibia lead concentrations predict a steeper decline over time in performance on the cognitive test in an occupational cohort of men, which is more pronounced with aging. Although circulating lead in blood may predict performance on some cognitive tests, the change in cognition over time is most associated with cumulative exposure to lead.

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