Cumulative Lead Exposure and Cognitive Performance Among Elderly Men

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Background: Recent evidence suggests that cumulative lead exposure among adults in nonoccupational settings can adversely affect cognitive function. Which cognitive domains are affected has not been explored in detail.

Methods: We used nonlinear spline regressions and linear repeated-measures analysis to assess the association between scores on a battery of cognitive tests over time and both blood and bone lead concentrations in the Normative Aging Study, a cohort of community-dwelling elderly men. Bone lead was measured from 1991 through 1999 with K-shell x-ray fluorescence. A total of 1089 men with a mean (±standard deviation) age of 68.7 (±7.4) years with blood lead measurements, 761 of whom also had valid bone lead measurements, completed at least one of a battery of cognitive tests. Approximately 3.5 years later, 69% of the men had at least one repeat test. Cognitive testing was performed from 1993 through 2001.

Results: On a cross-sectional basis, there was little association between blood or bone lead and cognitive test scores. Change in performance over time on virtually all tests worsened as bone lead increased, with the most robust effects on performance and reaction time scores on visuospatial/visuomotor tests.

Conclusions: Low-level cumulative exposure to lead in nonoccupational settings may adversely affect cognitive function, particularly in the visuospatial/visuomotor domain.

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In the next 50 years, the percentage of Americans over the age of 75 years is expected to double and the number with Alzheimer disease (AD) to triple.[1,2] Mild cognitive impairment is more prevalent than AD and is receiving increasing attention, not only as a possible intermediate stage on the path to AD, but as an important deficit in its own right.[3] Significant benefits could result from a better understanding of modifiable risk factors for subclinical cognitive impairment, because this condition may be the most amenable to prevention and treatment. Exposure to lead may be one such modifiable risk factor. Even at very low levels, lead is associated with worse cognitive function in children.[4] Adults exposed at high levels, often occupationally, have also been found to have impaired cognitive function.[5] Few studies, however, have assessed such associations in general adult population cohorts with nonoccupational exposures.

We have previously found that cumulative lead exposure is associated with worse performance and worse change in performance over time on the Mini-Mental State Examination (MMSE) in a nonoccupational cohort of elderly men.[6,7] Although the MMSE assesses abilities in several domains, it is not designed to distinguish effects in different domains of cognitive abilities. Several studies have examined the association in occupational cohorts between cumulative lead exposure and cognitive function using batteries of cognitive tests,[8–15] but only one small preliminary study has done this in a nonoccupational setting.[16] One other study examined scores on several cognitive tests in a nonoccupational cohort of elderly women, but only in cross-sectional

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association with concurrent blood lead concentration among a rural subgroup.[17]

We extended our previous cross-sectional analysis[16] to examine a much larger number of subjects and the change in test performance over time to examine the effects of both concurrent and cumulative lead exposure on cognitive function over time in a variety of functional domains. Exposure to lead was assessed by measuring blood and bone lead concentrations among participants in the Department of Veterans Affairs (VA) Normative Aging Study, a cohort of elderly U.S. men with lead exposure similar to the general population.

METHODS

Study Population

This research was conducted on a subgroup of the VA Normative Aging Study, a multidisciplinary longitudinal study of aging in men established in 1963.[18] This cohort and the subgroup on whom bone lead measures were taken have been described in detail elsewhere.[19] Briefly, healthy men from the general population in the greater Boston, Massachusetts, area were recruited in the 1960s. These men reported for medical examinations every 3 to 5 years, at which time they underwent clinical examinations and completed extensive health- and lifestyle-related questionnaires. The attrition rate for all causes has been $<1\%$ annually and the response rate to mailed questionnaires that supplement onsite examinations has been $>80\%$.

From 1991 through 1999, 876 (68%) of 1285 active participants gave informed consent for a K-shell x-ray fluorescence (KXRF) measurement of lead content in the tibia and patella. Cognitive testing was begun in 1993 with 91% of all participants with bone lead measures having completed at least one round of cognitive testing. During this time, blood collected at onsite visits was analyzed for lead concentration. Blood lead was measured for 99% of participants taking cognitive tests for the first time. The research here was approved by the Human Subjects Committees of the Boston VA Healthcare System, the Brigham and Women's Hospital, and the Harvard School of Public Health.

Bone Lead Levels Measured by K-shell X-ray Fluorescence

Bone lead measurements were taken at 2 anatomic sites, the midtibial shaft and the patella, with an ABIOMED KXRF instrument (ABIOMED, Danvers, MA) as described previously.[20] A 30-minute measurement was taken at the midshaft of the left tibia and another one at the left patella after each region had been washed with a 50% solution of isopropyl alcohol. The tibial midshaft was taken as the midpoint between the tibial plateau and the medial malleolus. The KXRF beam collimator was sited perpendicular to the flat bony surface of the tibia and at 30° in the lateral direction for the patella. Tibia and patella bone lead measurements with estimated uncertainties greater than 10 and 15 μg/g bone, respectively, were excluded because these measurements usually reflect excessive subject movement during the measurement.

Blood Lead Levels

On the same day as the cognitive testing, fresh blood for lead measurement was taken in a special lead-free tube containing EDTA and was sent to ESA Laboratories (Chelmsford, MA). Blood samples were analyzed by Zeeman background-corrected flameless atomic absorption (graphite furnace). The instrument was calibrated before use with National Bureau of Standards Blood Lead Standard Materials. Ten percent of the samples were run in duplicate, 10% were controls, and 10% were blanks. Analysis of the blank and duplicate samples produced no evidence of external contamination or significant problems with reliability. In tests on reference samples from the Centers for Disease Control and Prevention, the coefficient of variation was 8% for concentrations below 30 μg/dL.

Cognitive Test Battery

The battery of cognitive tests included measures of sustained attention, perceptual speed, memory, language, and visuomotor ability. These tests were taken from several different batteries, including the Neurobehavioral Evaluation System 2 (NES2),[21] the Wechsler Adult Intelligence Scale-Revised (WAIS-R),[22] the Consortium to Establish a Registry for Alzheimer disease (CERAD) battery,[23] the MMSE,[24] and the developmental test of visual-motor integration (VMI).[25] The majority of these tests were the subject of a previous report among a much smaller sample of subjects from the Normative Aging Study.[16] The only additional test is delayed word list recall (CERAD), in which the score is the sum of words recalled from a list of 10 words presented (one by one on a computer screen) approximately 5 to 10 minutes earlier. A subset of tests was administered only to the first 524 participants: continuous performance (NES2), pattern memory (NES2), vocabulary (WAIS-R), and the Boston naming test (CERAD). For all participants who reported for their triennial examination, the following tests were administered: pattern comparison (NES2), digit span backwards (WAIS-R), word list memory (CERAD), delayed word list recall (CERAD), constructional praxis (copying of figures taken from CERAD, VMI, and MMSE), and verbal fluency (CERAD). These examinations were approximately 3.5 (standard deviation = 1.1) years apart.

Data Analysis

The bone lead measurement closest in time to the date of a given cognitive test visit was assigned to that visit. Approximately 93% of these were within 4 years of the cognitive test visit. The half-life of trabecular (eg, patella) bone lead may vary by age and previous exposure; in the Normative Aging Study cohort, it has been estimated at 8 years, and that of cortical (eg, tibia) bone lead at much longer times.[26] Identical analytic procedures were followed for all bone and blood lead measurements collected over time.

We first checked for nonlinear associations between cognitive test score and individual lead biomarkers. We ran generalized additive models (GAMs) using the R software package[27] with penalized spline terms for the lead biomarker, age, and (for models of bone lead) the years between bone lead measure and the date of the first cognitive test visit. (The

GAM function in R does not have the same difficulties with standard error estimation found in the GAM function in S-PLUS [Insightful Corp., Seattle, WA].) These models were run both for cross-sectional analyses of scores at the first cognitive testing visit and the difference in score between test visit number 2 and number 1 for each test additionally adjusting for education (<12 years, 12 years, 13–15 years, 16+ years), smoking status (never, former, current), and alcohol intake (grams/day; none and quartiles of consumption). For the difference models, additional adjustment was made for the number of years between the 2 tests. If smoothed terms for the lead biomarkers were significant at a 95% level of confidence, their difference from a linear term was assessed with a likelihood ratio test. The influence of extreme values of exposure was assessed using the generalized extreme-studentized-deviation (ESD) many-outlier method[28] to remove extreme outliers of bone lead. Subsequent analyses using linear regression methods were performed using SAS version 8.12 (SAS Institute, Cary, NC).

For the cross-sectional analyses, we used ordinary least squares regression. For those tests that were administered more than once, we used the baseline cognitive test score only. For the longitudinal analyses, we used repeated-measures analyses with an unstructured covariance matrix to account for correlation in repeated testing of an individual subject. Repeated-measures models for bone lead included a main effect term for lead as well as an interaction term between bone lead at the first test visit and number of years between the cognitive tests. The coefficients from this interaction term indicate the associations between bone lead and change over time in cognitive test scores. Longitudinal analyses were not done for blood lead because blood lead has a half-life of approximately 30 days and an influence on change in cognitive test score over an average of approximately 3 and a half years did not seem biologically plausible. In addition to the covariates listed here, we also ran models additionally adjusting for computer experience (yes/no), English as a first language (yes/no), and quintile of physical activity (kilocalories/week), the latter of which was based on the subject's responses on his last 3 questionnaires to reduce measurement error. Both age and age squared were included in linear regression models to improve control of confounding by age. For all analyses of cognitive test scores, we calculated 95% confidence intervals (CIs). Interquartile ranges (IQRs) were the difference between values at the 75th and 25th percentile levels of a given distribution.

RESULTS

A total of 1089 participants in the Normative Aging Study with blood lead measurements (760 with patella and 761 with tibia bone lead measurements) completed at least one cognitive test. Table 1 shows the distribution of the lead biomarkers by categories of the covariates. At baseline, the mean age of the men (±SD) was 68.7 years (±7.4). The median baseline blood, patella, and tibia lead concentrations were 5 μg/dL (IQR = 3–6), 25μg/g bone mineral (17–37), and 20 μg/g bone mineral (13–28), respectively. As has been reported previously,[6] the correlation between patella and tibia bone lead was high (Spearman correlation = 0.66). Those subjects who had a second cognitive test had slightly lower patella and tibia lead (ranging from 0.0 to −1.9 μg/g and −0.8 to −1.6 μg/g, respectively, for the different tests) and slightly higher test scores on all tests of cognitive function than those subjects without a second test.

In analyses of complete data, 3 associations were found to be significantly nonlinear. The first was the cross-sectional association between blood lead and vocabulary scores, which decreased little with increasing blood lead levels until approximately 10 μg/dL, at which point they declined approximately one point for each μg/dL increase in blood lead concentration. The second was the cross-sectional association between tibia lead and the number of correct responses in the pattern memory test, which also varied little by tibia lead until concentrations exceeded approximately 40 μg/g bone mineral, at which point performance worsened by approximately one point for each 10-μg/g increase in tibia lead concentration up to 80 μg/g. These 2 nonlinear associations, however, were strongly influenced by a few subjects with the highest lead exposure measurements. When outliers—as identified with the ESD procedure (n = 5 [>15 μg/dL] in the blood lead analysis above and n = 9 [>66 μg/g bone mineral] in the tibia analysis)—were removed, the nonlinear associations did not persist.

The third nonlinear association was that between patella lead and the change over time of response latency on the pattern comparison test. When outliers in this analysis (n = 9; >89 μg/g bone mineral) were removed, the nonlinear association remained significant ($P = 0.009$) but was only marginally more significant ($P = 0.07$) than the linear association. The nonlinear association (Fig. 1) showed that latency times on the pattern comparison test became worse over time (ie, larger values or slower response latencies) up to approximately 60 μg/g bone mineral. At the higher patella bone lead concentrations, the association leveled off.

In linear regression analyses, the only significant cross-sectional association was between blood lead and scores on the test of vocabulary (Table 2). This result was dependent on those with the highest blood lead concentrations; excluding those identified as outliers by the ESD procedure (n = 5; >15 μg/dL) substantially weakened this association (effect estimate = −0.68; 95% CI = −1.59 to 0.23; $P = 0.15$). The cross-sectional analyses with bone lead biomarkers showed no important associations (Table 3). The results were not appreciably different when these analyses were done with repeated measures for those cognitive tests given more than once.

The longitudinal associations between measures of lead in both patella and tibia bone and change over time were inverse on almost all cognitive tests (Table 4); higher bone lead was associated with more decline in performances over time. The most robust associations were the following: those between patella lead and constructional praxis score (more decline in scores with higher lead) and response latency on the pattern comparison test (greater increase in latencies with higher lead); and those between tibia lead and response latency on the pattern comparison test (greater increase in latencies with higher lead) (Table 4). The associations be-

TABLE 1. Baseline Lead Levels* by Characteristics of Subjects

	Blood Lead (n = 1089)		Patella Lead (n = 760)		Tibia Lead (n = 761)	
	Percent Distribution	Lead Levels (μg/dL)	Percent Distribution	Lead Levels (μg /g)	Percent Distribution	Tibia Lead (μg/g)
Age (yrs)						
<60	11	4.6	10	18.9	10	13.4
60–64	23	4.9	24	24.2	24	18.1
65–69	25	5.3	26	29.8	27	21.9
70–74	23	5.3	23	33.8	23	25.4
75+	19	5.6	17	36.4	16	27.6
Education (yrs)						
<12	8	6.1	7	41.0	7	30.8
12	29	5.5	28	32.7	28	24.1
13–15	26	5.2	26	28.8	26	22.0
16+	37	4.7	39	24.7	39	18.6
Smoking status						
Never	29	5.0	30	26.3	30	20.0
Former	65	5.2	64	30.5	64	22.6
Current	6	5.6	6	29.6	6	21.0
Alcohol intake†						
None	26	4.9	27	29.7	26	21.9
1st quartile	17	4.3	17	24.7	18	20.2
2nd quartile	18	5.2	18	28.1	18	22.1
3rd quartile	18	5.3	18	30.8	18	22.4
4th quartile	18	6.3	18	32.0	18	22.1
Physical activity						
1st quintile	21	5.6	22	32.4	21	23.0
2nd quintile	19	5.1	20	28.7	21	22.2
3rd quintile	20	5.0	19	28.9	19	22.5
4th quintile	19	5.2	19	27.5	19	19.3
5th quintile	20	5.1	20	27.9	20	21.1
Computer experience						
Yes	38	4.8	39	25.9	38	19.9
No	58	5.4	58	31.1	59	23.1
First language English						
Yes	89	5.1	89.2	28.8	89	21.6
No	10	5.9	10.4	33.0	10	23.4

*All variables except age are age-adjusted by direct standardization to the entire cohort of each lead measure. Not all percentages add to 100 because of missing data.
†Quartiles are of those who consumed any alcohol.

tween patella and tibia lead and the change over time in the number of correct responses on the pattern comparison test (less decline in scores with higher lead) were substantially weakened when outliers were removed. The other associations were not materially affected when outliers for those analyses were removed.

These findings were not materially affected by additional adjustment for computer experience, English as a first language, and physical activity. Removing outliers using the ESD procedure did not materially affect any results other than those mentioned previously. None of the subjects had AD, which is associated with cognitive decline. If we excluded from our analyses subjects who were missing information for, or reported a history of, stroke (n = 9 and 7 for blood and bone lead analyses, respectively), myocardial infarction (n = 45 and 32, respectively), or diabetes (n = 78 and 63, respectively), the results were, in general, not materially affected (data not shown). The one exception was that the associations of higher patella and tibia bone lead with improved performance over time for the number of correct responses in the pattern comparison test were substantially weakened.

DISCUSSION

In this nonoccupational cohort of elderly men with repeated cognitive testing over an average interval of approximately 3.5 years, we found substantial associations between different lead exposure biomarkers and cognitive tests, pre-

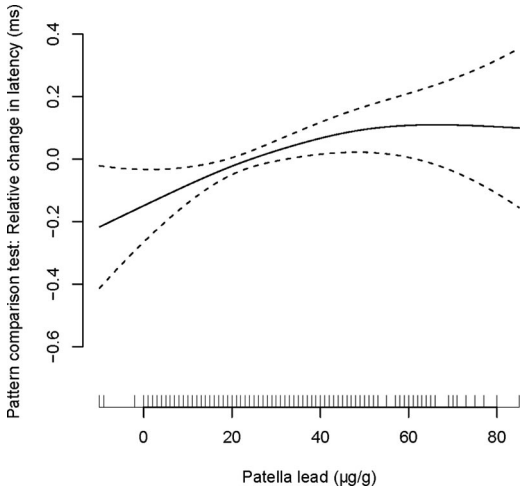

FIGURE 1. Nonlinear association between patella bone lead concentration and the relative change in response latency over time on the pattern comparison test (reference = 0 at mean of patella lead concentration) adjusted for age, age squared, education, smoking, alcohol intake, years between bone lead measurement and first cognitive test, and years between the cognitive tests. The 9 subjects with the highest patella lead concentrations (>89 μg/g bone mineral) as determined by the ESD procedure were removed. The estimate is indicated by the solid line and the 95% confidence interval by the dashed lines. The nonlinear association is significant at $P = 0.009$, and the difference from a linear association is marginally significant at $P = 0.07$. Patella lead concentrations of all individual subjects are indicated by short vertical lines on the abscissa.

dominantly in the visuospatial/visuomotor domains. Using cross-sectional analysis, higher blood lead concentration was associated with lower scores on tests of vocabulary, but this result did not persist when outliers were removed. Higher patella bone lead concentration was associated with greater decline in performance over time for both figure-copying skill and response latency in the pattern comparison test. Higher tibia bone lead concentration was associated with worse decline in performance over time for response latency in the pattern comparison test. Increasing bone lead was associated with improved performance over time for the number of correct responses in the pattern comparison test, although this result did not persist when outliers were removed or when exclusions were made on the basis of existing diseases. Cumulative lead exposure—as measured by lead in bone—was inversely related with change in scores over time on all other cognitive tests.

We have previously shown that bone lead concentration is associated with cognitive function both cross-sectionally[7] and longitudinally[6] as assessed with the MMSE. The MMSE, however, was designed as a screening tool for dementia and does not provide detail on particular cognitive domains that may be more or less affected. Our present results build on a previous cross-sectional study of a much smaller subset (n = 141) of the participants included in the present study[16] and is the only study of which we are aware that examines cumulative lead exposure and longitudinal change over time on a battery of cognitive function tests in a nonoccupational cohort of adults. The only other study to look at the association between lead exposure and a battery of cognitive tests among a nonoccupational cohort of adults used blood lead only as an exposure marker in examining this question among elderly women from either the Baltimore area (urban) or Monongahela Valley (rural) areas of Pennsylvania participating in the Study of Osteoporotic Fractures.[17] Substantial associations were found only among the rural women for whom blood lead was inversely associated with performance on a test of attention (Trailmaking B), a visuospatial test (digit symbol substitution from the WAIS-R), and reaction time tests, but not on an incidental memory test nor a test of fine motor control (grooved pegboard).

Several studies have examined the effect of lead on cognitive function in more highly exposed cohorts, usually in occupational settings. Acute exposures to high levels of lead among adults has consistently been associated with cognitive deficits in the domains of executive function/attention, memory, reaction time, visuospatial skills, and motor functioning.[13,29–31] Fewer studies have examined the association between cumulative lead exposure and cognitive function in these populations, partly because of the difficulty in obtaining good biomarkers for cumulative exposure.[8] More recent studies have examined this issue using KXRF technology to measure lead in bone. The majority of these studies were only cross-sectional and measured lead in tibia bone.[9–11,13,15] In general, the domains that were most consistently found to be inversely associated with tibia bone lead concentration were executive function/attention and visuospatial/visuomotor tasks, although associations with verbal and memory tasks were also noted. Two of the studies did not find any significant associations,[11,13] although in one of these, calcaneal bone lead (trabecular bone similar to patella) was also measured and found to be inversely associated with performance on a visuospatial task.[11] The only studies to look at change in performance over time in association with bone lead found inverse associations between tibia bone lead and, in particular, tests of executive function/attention and manual dexterity.[12,14] Of note, although decline in figure-copying performance over time was not strongly associated with tibia bone lead among former lead workers (who all had relatively high lead exposure), the lead workers declined more on this task than did a group of matched controls.[14]

Acutely, lead disrupts calcium-dependent enzymes and neurotransmitter release.[32–35] Resulting effects on synaptic transmission and plasticity could lead to circulating blood lead that impairs, for example, information storage mechanisms or processing speed, which has been suggested to impair performance on cognitive tests.[36] This latter could explain the inverse association we found between blood lead and vocabulary score.

A primary mechanism of damage resulting from cumulative exposure to lead is direct neuronal damage and death from oxidative stress.[37,38] Cardiovascular effects of lead[19] could also affect cognitive function as could long-term impairment of synaptic transmission and plasticity mentioned previously. The bone lead associations with response latency

TABLE 2. Cross-Sectional Analyses: Adjusted* Difference in Cognitive Test Score per 3 μg/dL (interquartile range) Higher Blood Lead Concentration

	No.	Effect Estimate per 3 μg/dL	(95% CI)	P
Attention/working memory/executive function				
Continuous performance (mean response latency of 2 best trials, ms)	509	0.08	(−4.92 to 5.07)	0.98
Digit span backward (total number of spans recalled)	961	−0.06	(−0.23 to 0.10)	0.47
Digit span backward (longest span recalled)	962	−0.04	(−0.14 to 0.09)	0.47
Verbal fluency test (total number of animals named)	1022	−0.02	(−0.35 to 0.31)	0.91
Short-term memory				
Pattern memory (response latency, ms)	513	−0.05	(−0.19 to 0.08)	0.45
Pattern memory (total number correct)	513	−0.12	(−0.40 to 0.16)	0.40
Word list memory (total number of words recalled)	1019	−0.02	(−0.27 to 0.23)	0.87
Delayed word list recall (total number of words recalled)	1017	0.08	(−0.05 to 0.20)	0.23
Visuospatial				
Constructional praxis (number correct)	1070	0.06	(−0.05 to 0.17)	0.30
Pattern comparison (response latency, ms)	1011	−0.01	(−0.12 to 0.09)	0.80
Pattern comparison (total number correct)	1011	−0.03	(−0.14 to 0.08)	0.60
Verbal/language				
Vocabulary (total number)	524	−1.26	(−2.08 to −0.44)	0.003†
Boston Naming Test (total number of objects named)	523	0.002	(−0.07 to 0.07)	0.96

*Adjusted for age, age squared, education, smoking, and alcohol intake.
†These results were not significant when bone lead outliers were removed from analysis.
ms indicates milliseconds.

TABLE 3. Cross-Sectional Analyses: Adjusted* Difference in Cognitive Test Score per Interquartile Range Higher Bone Lead Biomarker Concentration

	Patella				Tibia			
	No.	Effect Estimate per 20 μg/g	(95% CI)	P	No.	Effect Estimate per 15 μg/g	(95% CI)	P
Attention/executive function								
Continuous performance (mean response latency of 2 best trials, ms)	401	−3.8	(−9.29 to 1.69)	0.18	403	−0.93	(−6.81 to 4.95)	0.76
Digit span backward (total number of spans recalled)	702	−0.05	(−0.24 to 0.13)	0.58	703	−0.01	(−0.21 to 0.19)	0.92
Digit span backward (longest span recalled)	703	−0.04	(−0.16 to 0.07)	0.48	704	0.01	(−0.12 to 0.13)	0.90
Verbal fluency test (total number of animals named)	733	−0.22	(−0.62 to 0.17)	0.27	734	−0.27	(−0.70 to 0.16)	0.22
Short-term memory								
Pattern memory (response latency, ms)	406	0.02	(−0.14 to 0.17)	0.83	408	−0.03	(−0.19 to 0.14)	0.75
Pattern memory (total number correct)	406	−0.20	(−0.51 to 0.11)	0.19	408	−0.3	(−0.62 to 0.02)	0.08
Word list memory (total number of words recalled)	732	0.12	(−0.18 to 0.41)	0.43	733	0.12	(−0.20 to 0.32)	0.46
Delayed word list recall (total number of words recalled)	730	0.02	(−0.13 to 0.15)	0.79	731	0.14	(−0.02 to 0.17)	0.09
Visuospatial								
Constructional praxis (number correct)	749	0.09	(−0.23 to 0.06)	0.23	750	−0.10	(−0.26 to 0.05)	0.20
Pattern comparison (response latency, ms)	731	−0.02	(−0.14 to 0.11)	0.81	732	−0.03	(−0.17 to 0.11)	0.64
Pattern comparison (total number correct)	731	−0.09	(−0.21 to 0.04)	0.19	732	−0.11	(−0.25 to 0.03)	0.11
Verbal/language								
Vocabulary (total number)	409	0.044	(−0.90 to 0.98)	0.93	411	−0.42	(−1.42 to 0.58)	0.42
Boston Naming Test (total number of objects named)	411	0.046	(−0.03 to 0.12)	0.21	413	0.048	(−0.03 to 0.13)	0.23

*Adjusted for age, age squared, education, smoking, alcohol intake, and the years between bone lead measurement and cognitive test.

TABLE 4. Longitudinal Analyses: Adjusted* Difference in Change Over Time of Cognitive Test Score per Interquartile Range Higher Lead Biomarker Concentration

	Patella					Tibia				
	First Test No.	Second Test No.	Effect Estimate per 20 μg/g	(95% CI)	*P*	1st Test No.	2nd Test No.	Effect Estimate per 15 μg/g	(95% CI)	*P*
Attention/working memory/ executive function										
Digit span backward (total number of spans recalled)	702	412	−0.028	(−0.09 to 0.03)	0.36	703	405	−0.039	(−0.10 to 0.02)	0.22
Digit span backward (longest span recalled)	703	413	−0.010	(−0.05 to 0.03)	0.61	704	406	−0.022	(−0.06 to 0.02)	0.27
Verbal fluency test (Total number of animals named)	733	491	−0.086	(−0.20 to 0.03)	0.14	734	485	−0.040	(−0.16 to 0.08)	0.51
Short-term memory										
Word list memory (total number of words recalled)	732	486	−0.081	(−0.17 to 0.005)	0.06	733	480	−0.028	(−0.12 to 0.06)	0.55
Delayed word list recall (total number of words recalled)	730	480	−0.024	(−0.07 to 0.02)	0.29	731	474	−0.032	(−0.08 to 0.02)	0.20
Visuospatial										
Constructional praxis (number correct)	749	515	−0.067	(−0.11 to −0.02)	0.0041	750	510	−0.030	(−0.08 to 0.02)	0.22
Pattern comparison (response latency, ms)	731	446	0.073	(0.04 to 0.12)	0.0008	732	441	0.079	(0.04 to 0.12)	0.0004
Pattern comparison (total number correct)	731	446	0.040	(0.002 to 0.08)	0.042†	732	441	0.042	(0.002 to 0.08)	0.038†

*Adjusted for age, age squared, education, smoking, alcohol intake, years between bone lead measurement and first cognitive test, and years between the cognitive tests.
†These results were not significant when bone lead outliers were removed from analysis.

in the pattern comparison test may suggest an effect of cumulative lead exposure on reaction time in our cohort, but it is possible that the slower reaction times are the result of visuospatial deficits affecting the ability to make the pattern comparison. Although it has been suggested that lead may preferentially accumulate in particular areas of the brain such as the hippocampus, more recent animal studies suggest that the accumulation of lead in brain is generally uniform.[39] Either way, the visuospatial/motor deficits we found seem unlikely to result from preferential accumulation of lead in posterior regions of the brain that tend to subserve these functions. Given that occupational studies with higher lead exposure find deficits in more functional domains and the fact that we found bone lead to be inversely associated—even if not strongly so—with almost all cognitive tests, a more likely explanation may be that neural systems subserving visuospatial/motor functions are more sensitive to perturbation by the effects of lead than other cognitive functions.

There are limitations of this study that should be considered. First, although we attempted to control for a number of factors that might affect lead concentrations and cognitive performance such as age and education, test performance may be determined by many factors. Like in any epidemiologic study, our results could be biased to the extent that we did not control for such factors. Second, in repeated-measures analyses, a number of subjects did not take all the tests twice. The average differences in bone lead levels between those who did and did not have a second test were very small (<1.9 μg/g bone), however, suggesting that any possible bias is likely to be minor. Lastly, our results for change in cognitive test scores over time are based on an average of only 3.5 years between tests. It is possible that follow-up over longer periods of time would reveal other (perhaps stronger) effects.

In summary, our results suggest that in a nonoccupational, general population setting, cumulative exposure to lead can adversely affect performance on cognitive tests in the visuospatial/visuomotor domain. Rather than being a pattern of effects that is distinct from those reported after occupational exposures, these effects appear to represent a subset of those reported to be affected by occupational exposures and may represent cognitive domains that are more sensitive to the effects of lead exposure.

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