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Cumulative Lead Exposure and Prospective Change in Cognition among Elderly Men

The VA Normative Aging Study

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Lead exposure has been found to affect cognitive function in several different populations. Whether chronic low-level environmental exposure to lead results in cognitive decline among adults has not been examined. The authors assessed the relation between biomarkers of lead exposure and change in Mini-Mental State Examination (MMSE) scores in the Normative Aging Study, a cohort of elderly US men. Bone lead was measured with K-shell x-ray fluorescence. A total of 466 men aged 67.4 (standard deviation, 6.6) years took the MMSE on two occasions that were an average of 3.5 (standard deviation, 1.1) years apart during the period 1993–2001 and had bone lead concentrations measured during the period 1991–2002. A one-interquartile range (20 μg/g of bone mineral) higher patella bone lead concentration was associated with a change in MMSE score of –0.24 (95% confidence interval: –0.44, –0.05) after adjustment for age, education, smoking, alcohol intake, and time between MMSE tests. This effect is approximately equivalent to that of aging 5 years in relation to the baseline MMSE score in study data. The association with tibia lead was weaker and that with blood lead was absent. The data suggest that higher patella bone lead levels, a marker of mobilizable accumulated lead burden, are associated with a steeper decline over time in performance on the MMSE test among nonoccupationally exposed elderly men.

bone and bones; lead; neuropsychological tests; prospective studies

Abbreviations: KXRF, K-shell x-ray fluorescence; MMSE, Mini-Mental State Examination; VA, Veterans Administration.

The percentage of Americans over the age of 75 years is expected to increase from 6 percent in 1997 to 11 percent in 2047 (1), and the number of persons with cognitive impairment will likely increase dramatically in the coming years (2). Cognitive declines and impairment are observed frequently among the elderly and are a threat to the quality of life of affected individuals and their caregivers. Impaired cognition among adults is associated with functional decline in activities of daily living, increased risk of injury to self and others, associated demands on caregivers, and an increased risk of mortality (3–7). Although not as severe, mild cognitive impairment is increasingly being recognized as a transitional state between normal aging and dementia (8, 9). While recent research is advancing our understanding of methods to delay established dementia, currently relatively little work is aimed at detecting modifiable risk factors associated with subclinical cognitive impairment, a condition which may be the most amenable to preventive and treatment interventions.

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Extensive research has implicated lead exposure, even at very low levels of exposure, in cognitive impairment among children (10–13) and among occupational cohorts of adults with higher levels of exposure (14–18). The effect of low-level environmental (nonoccupational) exposure to lead on cognitive function in adults has received much less research attention. A few cross-sectional studies have found an inverse relation between blood lead levels and cognitive function in nonoccupationally exposed adult populations (19–21), although one such study did not (22). Cognitive impairment as a result of chronic low-level environmental exposure, however, may be more a function of cumulative lead exposure, which is better reflected by bone lead measures. Two of the cross-sectional studies also looked at bone lead and also found inverse associations with cognitive function (20, 21). The only longitudinal study to examine bone lead and decline in cognitive function was done among former organolead workers and found that estimated historical peak tibia lead levels from levels measured after workplace exposures had ended predicted declines in scores on several neuropsychological tests (23). The association between longitudinal decline in cognitive function among adults and cumulative exposure to low-level environmental (nonoccupational) levels of lead as measured by levels in bone has not been examined. To do this, we assessed the association between lead levels in bone and changes in Mini-Mental State Examination (MMSE) scores among participants in the Normative Aging Study, a cohort of elderly US men with lead exposure similar to that of the general population.

MATERIALS AND METHODS

Study population

This research was conducted on a subgroup of the Veterans Administration (VA) Normative Aging Study, a multidisciplinary longitudinal study of aging in men initiated in 1963 by the Veterans Administration (currently known as the Department of Veterans Affairs) (24). The research herein was approved by the human subjects committees of the Boston VA Medical Center, the Brigham and Women's Hospital, and the Harvard School of Public Health. This cohort and the subgroup on whom bone lead measures were taken have been described in detail elsewhere (25, 26). Briefly, the Normative Aging Study is based at the Boston VA Medical Center and has had an attrition rate for all causes of less than 1 percent annually and a greater than 80 percent response rate to mailed questionnaires that supplement on-site examinations. Normative Aging Study subjects reported for medical examinations every 3 years. During these visits, participants filled out questionnaires on smoking history, educational level, food intake, and other risk factors that may influence health. Beginning in 1991, those who gave their informed consent presented to the Ambulatory Clinical Research Center of the Brigham and Women's Hospital for a K-shell x-ray fluorescence (KXRF) measurement of lead content in the tibia and patella. Bone lead levels were measured between 1991 and 2002. If subjects had more than one bone lead measurement during this period (75 percent of subjects analyzed), the measurement performed closest to the date of the first cognitive testing was used for this analysis. Ninety-eight percent of these were within 3.5 years of the first MMSE test. The half-life of cortical (e.g., patella) bone lead may vary by age and previous exposure, but in the Normative Aging Study cohort it has been estimated at 8 years, and that of trabecular (e.g., tibia) bone lead has been estimated at much longer times (27). For all bone and blood lead measurements collected over time, identical analytical procedures were followed.

Beginning in 1993, Normative Aging Study participants underwent a series of cognitive tests, including the MMSE (28). The MMSE assesses abilities in several domains, including orientation to place and time, memory, attention, language, and ability to copy a design. The test is used primarily as a screening instrument for dementia and is widely used in epidemiologic studies (29). Correct responses are summed to give a maximum score of 30, and a score of 24 or more is considered within the normal range. Subjects who score 23 or less are at increased risk for dementia, although further testing is needed to determine if dementia is present (30). For this analysis, we did not include the question on county ("What county are we in?"), as counties in Massachusetts have little political meaning and are generally not known and, thus, not of diagnostic utility. The problems with this question on the MMSE battery have been discussed previously (30). Thus, for the current study, the maximum MMSE score was 29.

The Normative Aging Study is a closed cohort that initially consisted of 2,280 community-dwelling men who were aged 21–80 years at enrollment (24). Men with past or present chronic conditions (e.g., heart disease, cancer, diabetes, gout, asthma, sinusitis, bronchitis, and peptic ulcer), systolic blood pressure of greater than 140 mmHg, or diastolic blood pressure of greater than 90 mmHg at the time of enrollment (1961–1970) were excluded. Virtually all men who were still active participants when cognitive testing was introduced completed at least one MMSE test ($n = 1,025$). Of these, 753 agreed to have their bone lead measurements taken and had valid patella bone lead measurements. Our analyses of the effect of lead exposure on change in MMSE test scores are based on the 466 (62 percent) of these 753 men who took at least two MMSE tests. We have previously found little difference between those Normative Aging Study participants with MMSE data who did or did not have bone lead data (21).

Bone lead levels measured by KXRF

Bone lead measurements were taken at two anatomic sites, the midtibial shaft and the patella, with an ABIOMED KXRF instrument (ABIOMED, Danvers, Massachusetts) as described previously (31). The tibia and patella have been targeted for bone lead research because these two bones are primarily cortical and trabecular bone, respectively, with different ramifications in terms of toxicity (31). A 30-minute measurement was taken at the midshaft of the left tibia and at the left patella, after each region had been washed with a 50 percent 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 perpendicularly to the flat bony surface of the tibia and at 30 degrees in the lateral direction for the patella.

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 ethylenediaminetetraacetic acid and was sent to ESA Laboratories (Chelmsford, Massachusetts). Blood samples were analyzed by Zeeman background-corrected flameless atomic absorption (graphite furnace). The instrument was calibrated before use with blood lead standard materials from the National Bureau of Standards. Ten percent of the samples were run in duplicate, 10 percent were controls, and 10 percent were blanks. Analysis of the blank and duplicate samples found 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 ranged from 8 percent for concentrations below 30 μg/dl to 1 percent for concentrations higher than 30 μg/dl.

Data analysis

Tibia and patella bone lead measurements with estimated uncertainties greater than 10 and 15 μg/g of bone, respectively, were excluded as these measurements usually reflect excessive patient movement during the measurement (32, 33). Such procedures are standard in analysis of bone lead data (31). We used the generalized extreme studentized deviation many-outlier method (34) to remove extreme outliers among the continuous independent variables with a normal distribution, as has been done in previous analyses (20, 35–38). This procedure removed only 10 subjects with extreme tibia lead levels and only eight subjects with extreme patella lead levels. We also report results of analyses that included those subjects with extreme bone lead measurements.

We analyzed the association between change in MMSE score from the first to the second test and lead biomarker levels by regressing change on lead biomarker and other potential confounders. To check for possible nonlinear relations between change in MMSE score and continuous predictor variables, we ran generalized additive models using S-PLUS software (Insightful Corporation, Seattle, Washington) and included loess smoothing terms for the continuous variables, with optimal spans chosen on the basis of minimizing the Akaike Information Criterion (39) and a robust fitting algorithm for gaussian distributions of error terms. Significance at a 95 percent level of confidence of a nonlinear component of a term was based on the F statistic. Once extreme outliers were removed from the data, none of the variables had significant nonlinear components. Thus, linear models were run using PROC GENMOD in SAS software (SAS Institute, Inc., Cary, North Carolina) (40) with a normal distribution, identity link function, and empirical variance estimates. Data that included the extreme outliers were analyzed with generalized additive models run using S-PLUS software with significant nonlinear components of terms included. The potential confounding variables considered were age at first MMSE test, alcohol intake, and days between the two MMSE tests as continuous variables, as well as education (<12 years, 12 years, 13–15 years, ≥16 years), smoking status (never, former, current), computer experience (yes/no), and English as a first language (yes/no). We also included the residuals from a model of baseline MMSE score as a function of the same covariates to improve the precision of the parameter estimates. 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. Significance was tested using the likelihood ratio test comparing the models with and without the interaction terms. Univariate and bivariate analyses were performed using SAS version 8.12 software (40). Spearman's correlation coefficients were used to describe the bivariate relation between continuous variables. Interquartile ranges were the difference between values at the 75th and 25th percentile levels of a given distribution.

RESULTS

A total of 466 of the 753 (61.9 percent) Normative Aging Study participants with valid patella bone lead measurements completed two MMSE tests. Compared with participants who completed two MMSE tests, those who completed only one test were slightly older; more were ever smokers, had arthritis, had hypertension or reported hypertension medication use, and had slightly higher alcohol consumption; and slightly less had computer experience (table 1). Those with only one MMSE test had slightly higher bone lead levels but a similar average baseline MMSE score. There was evidence of a learning effect among the 466 participants who completed two MMSE tests, as their scores went up an average of 0.4 points (standard deviation: 1.9) on the second test.

Tables 2 and 3 show how lead levels vary across important characteristics. As expected, tibia and patella lead levels were very highly correlated, and both were also highly correlated with baseline blood lead level but not as strongly as they were with each other. As has been found previously, older men (table 2) and men who had fewer years of education (table 3) had higher lead levels. Having computer experience and English as a first language were both associated with lead levels, although the association with computer experience was the stronger of the two (table 3).

Having a one-interquartile range (20 μg/g of bone mineral) higher patella lead concentration was associated with a change in MMSE score of –0.24 (95 percent confidence interval: –0.44, –0.05) points when adjusting for age, education, smoking, alcohol intake, and time between MMSE tests (table 4). This is equivalent to the effect of 5.3 years of age on baseline MMSE score in our data. Having a one-interquartile range (14 μg/g of bone mineral) higher tibia lead concentration was associated with a change in MMSE score of only –0.17 (95 percent confidence interval: –0.38, 0.04) points when adjusting for the same variables (table 4). Including reported computer experience and English as a first language in the models had only minimal effects. If we excluded from our analyses subjects who had missing information for, or

TABLE 1. Baseline characteristics* by number of Mini-Mental State Examination tests, Normative Aging Study, Boston, Massachusetts, 1991–2002

	Subjects with only one MMSE† test (n = 287)	Subjects with two MMSE tests (n = 466)
Age, mean years (SD†)‡	70.1 (7.5)	67.4 (6.6)
Years of education, no. (%)		
<12	18 (6.3)	36 (7.7)
12	88 (30.7)	121 (26.0)
13–15	77 (26.8)	125 (26.8)
≥16	104 (36.2)	184 (39.5)
Smoking status, no. (%)‡		
Never	67 (23.3)	153 (32.8)
Former	182 (63.4)	286 (61.4)
Current	22 (7.7)	26 (5.6)
Computer experience, no. (%)‡	99 (34.5)	198 (44.0)
First language English, no. (%)	256 (89.2)	413 (88.6)
Use hearing aid, no. (%)	34 (11.9)	47 (10.1)
Arthritis in hands, no. (%)	99 (34.5)	130 (27.9)
Hypertension, no. (%)	138 (50.7)	213 (45.9)
Taking hypertension medication, no. (%)‡	119 (43.8)	161 (34.7)
Alcohol intake, median g/day (interquartile range)‡	14.2 (5.5, 34.0)§	10.2 (3.5, 19.1)¶
Patella lead, median μg/g (interquartile range)‡	27 (19, 40)	23 (15, 35)
Tibia lead,# median μg/g (interquartile range)‡	21 (15, 29)	19 (12, 26)
Blood lead, median μg/dl (interquartile range)**	5 (3, 7)	4 (3, 5)
Change in blood lead, median μg/dl (interquartile range)		–1 (–2, 0)
Baseline MMSE score, mean (SD)**	26.4 (2.1)	26.7 (1.7)
Change in MMSE score, mean (SD)		0.3 (1.9)
Years between MMSE tests, mean (SD)		3.5 (1.1)

* Not all sum to 100% because of missing data.
† MMSE, Mini-Mental State Examination; SD, standard deviation.
‡ Difference between subjects who took only one MMSE test and those who took two tests: $p < 0.05$.
§ Among 186 (64.8%) subjects reporting any intake.
¶ Among 324 (69.5%) subjects reporting any intake.
# Among subjects with tibia uncertainty of <10 (one MMSE test: n = 290; two MMSE tests: n = 463).
** Difference between subjects who took only one MMSE test and those who took two tests: $p < 0.1$.

reported a history of, stroke (n = 6 for both patella and tibia analyses), myocardial infarction (n = 16 for patella analyses; n = 15 for tibia analyses), or, additionally, diabetes (n = 42 for patella analyses; n = 41 for tibia analyses), the results only became slightly stronger (data not shown). In addition, if we excluded those who scored less than 23 on either test (n = 91 and n = 88 for patella and tibia analyses, respectively), the results were only minimally affected (data not shown). There was no significant interaction between age and either patella or tibia lead, and there was no significant interaction with education or time between MMSE tests.

The blood lead concentration at baseline did not show an association with change in MMSE score (table 4). These models included the change in blood lead concentration between the two tests because of the possibility that the blood lead concentration at the time of test taking may affect test performance, which also did not show an association with the change in MMSE score. This lack of significant association of the baseline blood lead measure was not a result of collinearity with the change in blood lead term, as removing the latter from the model led to only minimal change in the effect estimate for baseline blood and its precision. There was little difference in results when the models included bone lead concentration and the blood lead measures simultaneously. The precision of the estimates was reduced slightly, likely a result of correlation between the bone and blood lead measures.

The covariate-adjusted associations between patella and tibia lead and change in MMSE score using the fully adjusted model are shown in figures 1 and 2, respectively. Removing the highest tibia lead measurement had little effect on the parameter estimate. Results were similar when analyses included the outliers removed by the extreme studentized deviation procedure (including eight subjects

TABLE 2. Spearman's correlations among variables of 466 participants who took the Mini-Mental State Examination twice, Normative Aging Study, Boston, Massachusetts, 1991–2002

	Patella lead	Tibia lead	Baseline blood lead	Change in blood lead	Age	Years between MMSE† tests	Alcohol
Tibia lead	0.60***						
Blood lead	0.40***	0.34***					
Change in blood lead	–0.07	–0.02	–0.47***				
Age	0.25***	0.31***	0.15**	–0.08*			
Years between MMSE tests	–0.01	–0.01	–0.03	–0.15**	0.17**		
Alcohol	0.03	–0.04	0.06	–0.02	–0.07	–0.17**	
Baseline MMSE	–0.07	–0.09*	–0.03	0.03	–0.17**	0.02	0.08*

* $p \leq 0.1$; ** $p \leq 0.01$; *** $p \leq 0.0001$.
† MMSE, Mini-Mental State Examination.

with patella lead concentrations of ≥90 μg/g of bone and 10 subjects with tibia lead concentrations of ≥67 μg/g of bone). The association between patella lead and change in MMSE score showed a steeper inverse association at lower lead concentrations, but the extreme lead concentrations resulted in an unstable association above lead concentrations of approximately 70–75 μg/g, and the overall association showed a significant nonlinear component. The association with tibia lead remained linear and was slightly weaker than when the extreme concentrations were excluded. The excluded participants had lower average baseline MMSE scores than the average of the rest of the participants analyzed (MMSE score = 26.7) (table 1). Those with a patella lead measurement of ≥90 μg/g of bone had an average baseline MMSE score of 24.6, and those with a tibia lead measurement of ≥67 μg/g of bone had an average baseline MMSE score of 24.9.

DISCUSSION

In this cohort of 466 men, we found that cumulative exposure to lead—even at relatively modest levels—as assessed

TABLE 3. Mean lead levels and change in blood lead level from Mini-Mental State Examination test 1 to test 2 across categorical variables, Normative Aging Study, Boston, Massachusetts, 1991–2002

	Patella lead level (μg/g)	Tibia lead level (μg/g)	Baseline blood lead level (μg/dl)
Years of education			
<12	33.4 (14.3)*	25.3 (11.8)	5.4 (2.3)
12	32.0 (19.5)	22.7 (11.4)	5.6 (2.9)
13–15	25.4 (14.9)	19.1 (9.7)	4.6 (2.2)
≥16	22.6 (12.8)	17.5 (9.5)	4.5 (2.3)
p value	<0.0001	<0.0001	<0.0001
Smoking status			
Never	24.4 (13.9)	18.4 (10.3)	4.6 (2.4)
Former	27.8 (17.0)	20.7 (10.6)	5.0 (2.5)
Current	24.3 (12.1)	17.9 (8.9)	5.7 (2.8)
p value	0.07	0.07	0.08
Computer experience			
Yes	23.3 (14.3)	17.3 (9.8)	4.5 (2.4)
No	29.5 (16.7)	22.1 (10.6)	5.2 (2.6)
p value	<0.0001	<0.0001	0.0007
First language English			
Yes	26.0 (15.5)	19.5 (10.5)	4.8 (2.5)
No	30.2 (18.3)	21.8 (10.4)	5.6 (2.7)
p value	0.08	0.14	0.02

* Numbers in parentheses, standard deviation.

TABLE 4. Difference in change of Mini-Mental State Examination score associated with one interquartile range increment in lead measure, Normative Aging Study, Boston, Massachusetts, 1991–2002

Model	Parameter estimate					
	Patella lead, interquartile range increment of 20 μg/g (n = 455*)		Tibia lead, interquartile range increment of 14 μg/g (n = 451*)		Baseline blood lead,† interquartile range increment of 2 μg /dl (n = 559)	
	Estimate	95% confidence interval	Estimate	95% confidence interval	Estimate	95% confidence interval
Crude	–0.27	–0.44, –0.09	–0.23	–0.42, –0.04	0.01	–0.11, 0.13
Adjusted‡	–0.24	–0.44, –0.05	–0.17	–0.38, 0.04	–0.01	–0.13, 0.11
Complete§	–0.25	–0.45, –0.05	–0.19	–0.39, 0.02	–0.01	–0.13, 0.11

* Numbers are less than 466 because of missing alcohol, smoking, and (for tibia analyses) valid tibia lead data.
† The values shown are from models that included both of these blood lead measures simultaneously. There were more participants with blood lead data who also had taken two Mini-Mental State Examination tests.
‡ Adjusted for age, smoking, education, alcohol, and years between Mini-Mental State Examination tests.
§ Also adjusting for computer experience and English as a first language.

by measuring lead content in patella bone was associated with a worse change in MMSE score over an average of 3.5 years. The effect of an interquartile range higher level of patella lead was equivalent to that of approximately 5 years of aging in relation to the baseline MMSE score in our data. Although in a previous cross-sectional analysis those with higher bone lead levels showed a greater effect of age on the baseline MMSE score (21), we did not find an interaction between age and lead on decline in the MMSE score over an average of 3.5 years.

This is the first study of a longitudinal decline associated with lead exposure in a nonoccupational, general community population of elderly men. Our results corroborate and extend those suggested by several cross-sectional studies that found an inverse association between different measures of cumulative lead exposure and different tests of cognitive function in both occupational cohorts (15, 16, 18, 41–45) and general population cohorts (20, 21). One of the general population studies found that blood lead levels as low as 8 μg/dl were significantly associated with impairment on several neuropsychological tests among a cohort of rural women but not urban women (19). In the Normative Aging Study cohort, our group previously found that a higher blood lead level was associated with impairments on several neuropsychological tests (20). A study among an elderly population aged 75 years or more in Sweden did not find an association between blood lead level and MMSE scores (22), although our group found in the Normative Aging Study cohort that higher blood lead levels were associated with increased odds of scoring less than 24 on the MMSE, a traditional cutpoint for increased risk of dementia (21). The previous cross-sectional studies by our group also found that

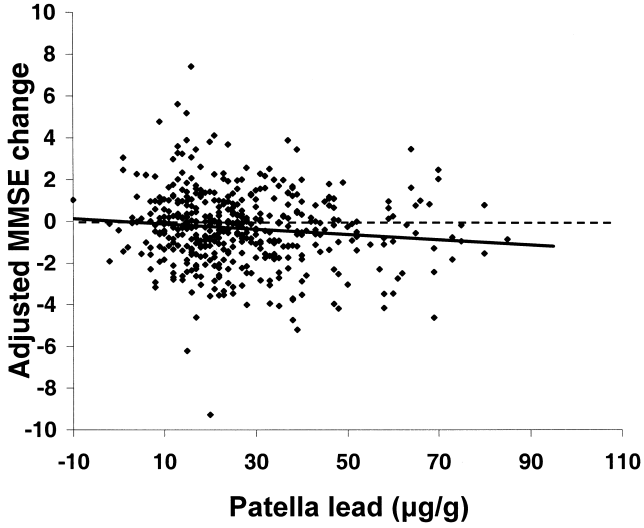

FIGURE 1. Adjusted differences in change in the Mini-Mental State Examination (MMSE) score by patella lead level (referent: patella lead = 0 μg/g of bone) among 455 subjects in the Normative Aging Study, Boston, Massachusetts, 1991–2002. Solid line indicates the linear trend.

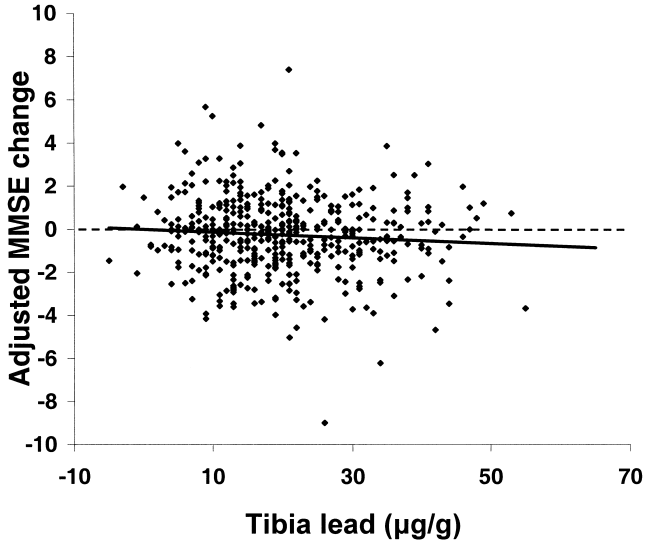

FIGURE 2. Adjusted differences in change in the Mini-Mental State Examination (MMSE) score by tibia lead level (referent: tibia lead = 0 µg/g of bone) among 451 subjects in the Normative Aging Study, Boston, Massachusetts, 1991–2002. Solid line indicates the linear trend.

a higher level of bone lead was associated with impairments on neuropsychological tests of visual memory and spatial copying (20) and increased odds of scoring less than 24 on the MMSE test (21).

Few longitudinal studies have examined the effects of lead exposure on change in cognitive function in adults, and they have all been in occupational cohorts. Reduction of very high levels of blood lead among organolead workers has been reported to improve scores on some neurocognitive tests (46, 47), and cumulative exposure to lead using serial blood lead measures among current organolead workers (48, 49) or KXRF measures of tibia lead among former organolead workers (23) has been found to have an adverse effect on scores on several neurocognitive tests. In the previous study of an occupational cohort using KXRF, Schwartz et al. (23) found results similar to ours, although in relation to tibia lead, for which a 15.7-µg higher tibia lead concentration per gram of bone (approximately 1 standard deviation) was associated with a decline in cognitive function that was equivalent to 5 extra years of age at baseline in their data. Also similar to our results, they found no relation between blood lead levels and subsequent decline in cognitive function. Our results suggest that such an inverse relation between lead exposure and aspects of cognitive function also exists in nonoccupational populations with much lower lifetime exposures to lead, although in our data patella lead, rather than tibia lead or baseline blood lead, was the most sensitive biomarker, which may be because patella lead represents a more readily mobilizable source of lead in bone.

There are both acute and more cumulative mechanisms by which lead could affect cognitive processing. Acutely, lead disrupts calcium-dependent neurotransmitter release (50–54) and interacts with calcium-dependent enzymes (55, 56), which can disrupt normal synaptic transmission and interfere with cellular mechanisms of plasticity. Via such effects, circulating blood lead could, for example, slow processing speed, which has been suggested to impair performance on cognitive tests (57). Lead exposure over longer periods of time appears to result in neuronal damage and potentially death from oxidative stress, both acting directly as an oxidative toxicant itself (58, 59) and indirectly by impairing the host response to oxidative toxicity (60). Chronic lead exposure has also been found to be a risk factor for hypertension (38), which may cause cerebrovascular disease leading to poor performance on cognitive tests.

Impaired cognition among adults is associated with an increased risk of mortality, particularly following acute medical events such as myocardial infarction (6, 7), as well as functional decline in activities of daily living (5). Mild cognitive impairment is also increasingly being recognized as a transitional state between normal aging and dementia (8, 9). It has been estimated that subjects so affected tend to progress to dementia or Alzheimer's disease at a rate of 10–15 percent per year (61). In a recent study, Alzheimer's disease patients with a baseline average MMSE score of 21 declined by an average of 2.8 points over 2 years (62). Although the effects of lead on the MMSE scores we report are much smaller, our population is much higher functioning. The relation between MMSE scores and assessments of activities of daily living, however, has been found to be close to linear, and even a 1-point increase in MMSE score has been associated with a significantly decreased risk of onset of any activities of daily living limitation over a 7-year follow-up period (63, 64).

There are limitations of this study that should be considered. First, while we attempted to control for a number of factors that might affect lead concentrations and changes in MMSE test performance such as age and education, test performance may be determined by many factors. As in any epidemiologic study, our results could be biased to the extent

that we did not control for such factors. Second, bone lead data were available for about 73 percent of all Normative Aging Study participants who took the MMSE test. However, we have previously found very little difference between those participants with MMSE data who did or did not have bone lead data (21). Thus, we believe that potential bias from this aspect of participation would not have appreciably affected our findings. Of those with bone lead and MMSE data, about 62 percent took the MMSE test at least twice. Normative Aging Study participants who took the MMSE test only once were slightly older (and slightly more were arthritic and had or were taking medication for hypertension), and they had slightly higher lead levels than Normative Aging Study participants who took the MMSE test twice (table 1). However, because cognitive decline increases with age (and presumably worse health), bias from these differences would likely have been against the relation we found, and the effect of lead on cognitive decline may be even more pronounced.

It is well known that change in a measurement over two tests is inversely correlated with the first of the two measurements because of regression to the mean (65, 66). We did not adjust for baseline MMSE score in our models, as this regression to the mean can bias results in observational studies, falsely creating an association of the type we found (66, 67). An inverse correlation between baseline MMSE score and change in MMSE score is also introduced by a ceiling effect that is a result of our MMSE measure's having a maximum of 29. The average score at baseline was almost 27, and because a learning effect led to scores generally being slightly higher at the second test, participants who scored well on their first test could not increase their score at their second test as much as participants who scored less well on their first test. Because MMSE scores are inversely correlated with bone lead levels cross-sectionally (21), the combination of the ceiling and learning effects in fact biases against finding the inverse association that we found between bone lead levels and change in MMSE scores. Thus, the true associations may be stronger than those we report.

When we included the few subjects (patella analyses: n = 8; tibia analyses: n = 10) with extreme bone lead concentrations, there was generally the same relation between bone lead and change in MMSE score as was seen when the subjects with extreme concentrations were excluded. In analyses including the subjects with extreme bone lead measures, however, the bone lead-change in MMSE relation became very unstable at the high lead levels. The instability at higher lead levels may be related to the ceiling effect, since the excluded subjects had lower baseline MMSE scores and thus would have had more room for improvement at the second test as a result of any learning effect. We also cannot rule out a survivor effect. It is possible that many of the original Normative Aging Study subjects with higher bone lead levels who died and could not participate in MMSE testing died partially as the result of worse health related to very high lead exposure. Those with high lead levels who were still alive to have bone lead measurements and MMSE tests may preferentially be people less susceptible to the adverse cognitive effects of lead.

In summary, our data suggest that higher patella lead concentrations predict a steeper decline over time in performance on the MMSE test in a nonoccupational cohort of men. While circulating lead in blood may predict performance on some cognitive tests, we found that the change in MMSE test performance over time is related to cumulative exposure to lead.

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