Relations of Bone and Blood Lead to Cognitive Function: The VA Normative Aging Study

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PAYTON, M., K. M. RIGGS, A. SPIRO III, S. T. WEISS AND H. HU. Relations of bone and blood lead to cognitive function: The VA Normative Aging Study. NEUROTOXICOL TERATOL 20(1) 19–27, 1998.—The relationship between performance on cognitive tasks and circulating levels of lead in blood and accumulated levels of lead in bone was examined in 141 middle-aged and elderly men from a longitudinal study of aging. The mean (SD) blood lead level was low [5.5 (3.5) mg/dl], and mean patella and tibia lead levels were 31.7 (19.2) and 22.5 (12.2) mg/g bone mineral, respectively. Cognitive tests measured attention, perceptual speed, memory, language, and spatial copying. Regression models, adjusted for age and education, demonstrated that men with higher levels of blood lead recalled and defined fewer words, identified fewer line-drawn objects, and required more time to attain the same level of accuracy on a perceptual comparison test as men with the lowest level of blood lead. Men with higher levels of bone (tibia) lead copied spatial figures less accurately; men with higher levels of bone (tibia) lead had slower responses for pattern memory. These findings suggest that low levels of lead contribute to impairments in cognitive function among elderly men. © 1998 Elsevier Science Inc.

ALTHOUGH the adverse health effects of lead have been known for centuries, they continue to pose a significant public health problem. Studies of persons with lead poisoning indicate that exposure to inorganic lead impairs central nervous system function (18). Early symptoms and signs of lead poisoning often suggest encephalopathy. High-level lead exposure in adults and children has been associated with deficits in memory and intellectual functioning (4–7,12,19,21,35,50,58,64), attention and concentration (4,40,55), and speed and psychomotor performance (4,16,22,24,29,56).

With the recent decline in environmental lead exposure (41), more subtle signs, such as mild deficits in cognitive function, have been observed. Much evidence supports the hypothesis that blood lead is associated with decreased cognitive performance in workers with moderate exposure (8,15,23,44), and in children with mild to moderate levels of lead exposure (11,17,33,39,51). However, the possible neurotoxic effects of low levels of lead exposure in adults have received less attention (38). Although decline in certain measures of cognitive function is inevitable, levels of cognitive performance may be associated with lead concentration. It is possible that some of the cognitive deficits often ascribed to aging may actually result from exposures to toxic sources such as environmental lead. As suggested by Weiss and Spyker (60), exposure to...
toxic metals during early life can lead to cognitive deficits later in life. One explanation for later life deficits in cognitive function may be that toxins such as lead accelerate the rate of decline of functional capacity in the aging brain (60).

Lead stores in blood reflect acute exposure or transient physiological changes. In contrast, the human skeleton is generally regarded as the major storage site for lead (9,42), with lead stores in bone most likely representing accumulated exposure over time. Thus, lead in bone may reflect chronic exposure and may also serve as a biomarker for neurotoxicity long after blood lead stores have been depleted. Release of lead from bone into plasma, particularly in states characterized by increased bone turnover (e.g., hyperthyroidism and osteoporosis), may play an important role in lead-related chronic disease, long after environmental exposures have declined (20,53). No epidemiological studies have assessed whether accumulated lead in bone is associated with cognitive function in the elderly.

The objective of this research was to examine the relationship of lead to cognitive function in middle-aged and older men. A secondary objective was to assess whether accumulated lead in bone was a better biomarker for cognitive performance impairment than was lead in blood. The data were obtained as part of several ongoing investigations in the Normative Aging Study (NAS).

**METHOD**

Participants

The men tested in this study, most of whom were from the Greater Boston area, were participants in the NAS, a longitudinal study of aging men established in 1963 at the Veterans Affairs (VA) Boston Outpatient Clinic (10). The study cohort initially consisted of 2,280 community-dwelling men who were 21–80 years of age upon enrollment. At the time of enrollment in the NAS (1961–1970), men with past or present chronic conditions (such as heart disease, cancer, recurrent asthma, sinusitis, bronchitis, diabetes, gout, and peptic ulcer) or with a systolic blood pressure of >140 mmHg or a diastolic blood pressure of >90 mmHg were disqualified. NAS participants were reevaluated at 3–5-year intervals by means of a detailed core examination including medical history, routine physical examination, laboratory tests, and questionnaires.

Beginning in July 1988, a blood sample for lead analysis was collected at each visit. K-XRF bone lead measurements were begun in 1991 (25), and cognitive measurements in 1993 (43). Between April 1993 and March 1994, 358 men were seen at the VA Outpatient Clinic. Two hundred and seven men completed cognitive tests. Of these, 176 had blood lead measurements and 160 had patella and tibia measurements recorded. For this study, analysis was restricted to participants with data for all variables of interest (i.e., blood lead, patella lead, tibia lead, cognitive measures, age, and education). Information on one or more of the variables of interest was missing for 18 men. One man with a history of stroke was excluded. Thus, 141 men were included in the sample studied.

The research study was approved by human studies committees at the Boston VA Outpatient Clinic and at Brigham and Women’s Hospital in Boston. Written informed consent was obtained from all participants.

Clinic Visit

Participants reported to the clinic at 0800 h. Blood specimens for routine clinical analysis and for blood lead analyses were obtained. A thorough physical examination was conducted, age and number of years of education were ascertained, and a battery of cognitive tests was administered (43). Within approximately 6 weeks of the clinical exam, patella and tibia lead levels were measured at Brigham and Women’s Hospital.

**Measurements**

**Blood lead.** A 7-ml sample of venous blood was obtained from each participant in a special trace metal- and lead-free tube containing ethylenediaminetetraacetic acid. The blood specimen was analyzed for lead by Zeeman background-corrected flameless atomic absorption (graphite furnace) at ESA Laboratories, Inc. (Bedford, MA). The instrument was calibrated before use and checked after every 21 samples with blood lead standard materials from the National Institute of Standards and Technology. Blood lead specimens were digested with nitric acid at room temperature. The solution was centrifuged, and the supernant was poured into a sample cup. At least 10% of analyses consisted of blanks and 10% of spiked control specimens. To prevent lead contamination, all equipment was washed and soaked overnight with nitric acid and then rinsed with distilled water. After the last specimen had been analyzed, a complete calibration check was made. Repeated analyses of control specimens known to contain 5.7, 12.0, and 22.0 μg of lead/dl gave values of 5.53 ± 1.40, 11.83 ± 1.45, and 21.79 ± 1.54 μg/dl, respectively.

**Bone lead.** A K-XRF instrument (ABIOMED, Inc., Danvers, MA) was used to measure levels of lead in bone. The physical principles, technical specifications, validation, and quality control procedures for this (14,26–28) and other K-XRF instruments (21,31,54) have been described in detail elsewhere. Because the instrument provides a continuous unbiased point estimate of bone lead that oscillates around the true value, negative point estimates are sometimes produced when the true value is close to zero. To maintain the true shape of the concentration distribution and to provide a relative position of each participant’s bone lead concentration within the population, negative point estimates were not recorded to zero (32). The instrument also estimates the uncertainty associated with each measurement: this estimate is derived from a goodness-of-fit calculation of the spectrum curves and is equivalent to a single standard deviation.

Two bone lead concentrations were obtained from each participant. Each participant underwent a 30-min measurement from the left patella and a 30-min measurement from the midpoint between the plateau and the medial malleolus of the left tibia. The skin over the patella and the tibia was washed thoroughly with a 50% solution of isopropyl alcohol to prevent contamination. The K-XRF beam collimator was positioned perpendicular to the bone surface for the tibia and at 30° in the lateral direction for the patella. Patella and tibia lead were retained as separate variables rather than combining them into one composite index of accumulated lead exposure because the kinetics of lead differ between these two bones. Lead in the patella, which is composed mostly of trabecular bone, has a short half-life, whereas tibia, mostly cortical bone, has a longer half-life (42).

**Cognitive Tests**

The battery of cognitive tests included measures of sustained attention, perceptual speed, memory, language, and spatial copying, selected from several batteries. The NES2 (Neurobehavioral Evaluation System) was developed to assess cognitive effects in persons with occupational and envi-
rnonmental lead exposures (2,8,34,62). Other measures were selected from batteries used to assess cognitive status and changes in adults. These included selected tests from the WAIS-R (Wechsler Adult Intelligence Scale-Revised) scale (59) and the CERAD (Consortium to Establish a Registry for Alzheimer’s Disease) battery (37). Inclusion of additional tests in the cognitive battery was constrained by the time required for their administration. Each included test is described below.

Continuous performance (NES2). Participants press a button when they see a large letter S, but no other letter, on a computer monitor. The score is the mean response latency (milliseconds) for items in the best two of six trials (10 target items in each trial). Best trials are defined as trials on which no or minimal errors are made and for which the mean response latencies are the fastest.

Pattern comparison (NES2). Three patterns are presented on the monitor, from which the one different pattern is chosen. Two scores are obtained: the number of correct responses (maximum, 25) and the mean response latency (seconds) for correct decisions.

Pattern memory (NES2). One pattern is presented on the monitor screen; after a brief interval, three similar patterns are presented, from which the original pattern must be identified. Two scores are obtained: the number of correct responses (maximum, 25) and the mean response latency (seconds) for correct decisions.

Digit span backward (WAIS-R). The score is the total number of spans (maximum, 12) repeated correctly in a backward sequence.

Vocabulary (WAIS-R). Participants define words of increasing difficulty, which are scored according to quality of definition (maximum score, 70).

Word list memory (CERAD). The score used for this test is the sum of words (maximum, 30) recalled over three consecutive trials, in which the same 10 words are presented (at a rate of one word every 2.5 s) on the computer screen.

Constructional praxis (CERAD). Participants copy a circle, crossed rectangles, vertical diamond, and a cube. Copying accuracy is scored by CERAD criteria (maximum score, 11).

Boston naming test (CERAD short form). Participants identify 15 line-drawn objects by name (maximum score, 15).

Verbal fluency (CERAD). Participants name as many members of a category (animals) as possible within 1 min.

Data Analysis

Means and SDs were calculated for all variables of interest. Participants who had all covariates of interest and were included in the study were compared with other NAS participants examined during the same period but were missing one or more of the covariates of interest. Pearson correlation coefficients were computed among age, education, patella lead, tibia lead, and cognitive outcome measures. Smooth plots (50) were used to explore possible nonlinear relations between scores on cognitive tests and other variables; no appreciable nonlinearities were detected. All analyses were performed with Statistical Analysis System version 6.07 (48). We first examined the associations of potential confounding variables of age and education (1,8,45,47) with each cognitive measure and each lead variable. Multivariate linear regression models were constructed to predict patella, tibia, and blood lead. Each model separately examined the relation between each blood and bone lead level and each cognitive test, controlling for age and education. Final regression models were obtained by applying a backwards-elimination procedure that kept continuous variables with $p$-values $< 0.10$. The procedure terminated when all remaining variables met the above $p$-value criterion.

In a second model, all three lead levels (patella, tibia, blood) were entered together, with both age and education, using a backwards-elimination algorithm to determine whether a measure of cumulative past exposure (bone lead) was more strongly associated with each cognitive outcome than was a measure of recent exposure (blood lead).

Finally, because only 68% of 207 participants had bone lead measures, we also analyzed the larger sample ($n = 176$) of participants who had blood lead data and covariates of interest, but no bone lead measurements.

RESULTS

Means and SDs for variables of interest are shown in Table 1. An analysis of participants who were not included in the present study showed no significantly different characteristics from those participants who were included in the study. The mean level of blood lead (5.5 μg/dl) of the study participants was roughly similar to that (4.7 μg/dl) observed in the third National Health And Nutrition Examination Survey by Brody et al. (13) for non-Hispanic white men aged 50 and older. The levels of bone lead (patella, 31.7 μg/g; tibia, 22.5 μg/g) in the study participants were similar to those (32.1 and 21.6 μg/g, respectively) reported by Hu et al. (25) for 590 men from the NAS, from whom the present sample was drawn. Scores on the cognitive tests were generally in the average range for older adults. One exception was that NAS participants exhibited relatively poor spatial copying (Constructional Praxis), scoring lower than 90% of the CERAD normal aging controls described by Welsh et al. (61).

Table 2 presents Pearson correlations among lead measures, cognitive tests, age, and education. The two bone lead measures were more highly correlated than was either with blood lead. Older men had higher levels of lead on all three measures, but age was less strongly related to blood lead. Men with more education had lower levels of bone lead, but education was not related to blood lead.

Older men selected and recognized incorrect patterns more often on the Pattern Comparison and Pattern Memory tests; were slower at making correct decisions in these tasks; recalled fewer words on the Word List Memory Test; and named fewer animals on the Verbal Fluency Test. Men with more education defined more words or produced better definitions on the Vocabulary Test; recalled more words on the Word List Memory Test; and copied more designs correctly on the Constructional Praxis Test.

Table 3 presents results of the analyses of covariance. Each cognitive test was adjusted for the covariates of age and education, as identified in prior analyses, and the additional effect of each of the three lead levels was then examined. After controlling for age and education, scores on tests of perceptual speed, immediate visual memory, vocabulary, immediate verbal memory, and spatial copying skill were significantly related to one or more measures of lead. Men with higher levels of bone lead were slower at making correct decisions on the Pattern Comparison Test, and those with higher levels of tibia lead were slower at making correct decisions on the Pattern Memory Test. Men with higher levels of blood lead also performed less well than men with lower levels on the Vocabulary, Word List Memory, Constructional Praxis, and Boston Naming tests. Finally, men with higher levels of patella and of
tibia lead performed more poorly on the Constructional Praxis Test.

We used backwards-elimination regression to examine the simultaneous effects of patella lead, tibia lead, and blood lead, controlling for age and education. The inferences remained unchanged when all three lead components were entered together in the same regression model. Men with higher levels of blood lead were slower on Pattern Comparison, had poorer vocabulary, and recalled fewer words. Men with higher levels of tibia lead had slower responses on Pattern Memory and those with higher levels of both tibia and blood lead did worse on spatial copying. This is the only cognitive outcome with which two lead measures were associated.

Results of these models indicated that an increase of 10 µg/dl of lead in blood was associated with an increase of 0.8 s in the time required for a correct response on the Pattern Comparison Test, a decrease of 1.8 words recalled on the Vocabulary Test, a decrease of 0.2 point and 0.3 point, respectively, on the Constructional Praxis Test, and a decrease of 0.4 point on the Boston Naming Test. An increase of 10 µg/g of lead in the patella and the tibia was associated with a decrease of 0.2 point and 0.3 point, respectively, on the Constructional Praxis Test.

In the analysis utilizing only blood lead (n = 176) as the predictor variable, the mean (SD) blood lead level [5.5 (3.5) µg/dl] and covariates of interest, i.e., age [66.9 (6.9) years] and education level [14.1 (2.5) years] were similar to those found in the sample of participants who had data on all three lead indices. Although there was a slightly larger sample size when using only blood lead, there were no significant associations with any cognitive outcome measure other than those found in the analyses with all three lead indices.

**DISCUSSION**

We examined the relations between low levels of circulating lead in blood and accumulated lead in bone to cognition in older men. The low level of blood lead observed (mean = 5.5 µg/dl) confirmed that these men had very little ongoing environmental exposure to lead. We found, nevertheless, that blood lead level was a significant predictor of performance on various measures of speed, memory, and verbal ability. Both blood and bone lead levels were significant predictors of spatial copying skill, and tibia lead level was a significant predictor of pattern memory speed (Table 3). These relations persisted after adjustment for age and education. Our results support the hypothesis that even within this relatively low range of exposure, higher levels of both blood and bone lead were significantly associated with poorer performance on cognitive tests.

We also attempted to assess whether a measure of cumulative past exposure (i.e., bone lead level) was a better predictor of cognitive function than was a measure of recent exposure (i.e., blood lead level). Backwards-regression models that considered the three lead variables simultaneously indicated that blood lead was generally the strongest predictor of performance on most tests (Table 3). Bone lead and blood lead were significantly associated in these models with the same cognitive test in only one instance: Constructional Praxis. Nevertheless, for those tests with performance decrements significantly related to blood lead level, the same trends were observed.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Participants (N = 141)</th>
<th>Nonparticipants</th>
<th>N*</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Covariates</strong></td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>66.8 (6.8)</td>
<td>68.8 (7.9)</td>
<td>64</td>
<td>0.084</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.0 (2.6)</td>
<td>13.6 (2.4)</td>
<td>61</td>
<td>0.285</td>
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<tr>
<td><strong>Lead exposure</strong></td>
<td></td>
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<tr>
<td>Patella bone lead (µg/g bone mineral)</td>
<td>31.7 (19.2)</td>
<td>40.0 (22.7)</td>
<td>19</td>
<td>0.143</td>
</tr>
<tr>
<td>Tibia bone lead (µg/g bone mineral)</td>
<td>22.5 (12.2)</td>
<td>27.1 (17.6)</td>
<td>19</td>
<td>0.283</td>
</tr>
<tr>
<td>Blood lead (µg/dl)</td>
<td>5.5 (3.5)</td>
<td>5.2 (2.4)</td>
<td>62</td>
<td>0.550</td>
</tr>
<tr>
<td><strong>Cognitive Tests</strong></td>
<td></td>
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<tr>
<td>NES2 test</td>
<td></td>
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<tr>
<td>Continuous Performance (ms)</td>
<td>341.5 (55.8)</td>
<td>337.4 (48.4)</td>
<td>44</td>
<td>0.637</td>
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<tr>
<td>Digit Span Backward (total No. correct)</td>
<td>5.3 (1.4)</td>
<td>5.2 (1.1)</td>
<td>48</td>
<td>0.635</td>
</tr>
<tr>
<td>Pattern Comparison (s/correct decision)</td>
<td>23.9 (1.4)</td>
<td>23.7 (2.0)</td>
<td>48</td>
<td>0.382</td>
</tr>
<tr>
<td>Pattern Memory (s/correct decision)</td>
<td>5.7 (1.5)</td>
<td>5.6 (1.3)</td>
<td>46</td>
<td>0.842</td>
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<tr>
<td>WAIS-R test</td>
<td></td>
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<tr>
<td>Digit Span Backward (total No. correct)</td>
<td>5.1 (2.2)</td>
<td>4.7 (2.2)</td>
<td>48</td>
<td>0.323</td>
</tr>
<tr>
<td>Vocabulary (verbal ability)</td>
<td>50.3 (9.7)</td>
<td>50.8 (8.9)</td>
<td>49</td>
<td>0.768</td>
</tr>
<tr>
<td>CERAD test</td>
<td></td>
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<tr>
<td>Word List Memory (total No. recalled)</td>
<td>19.4 (3.7)</td>
<td>18.2 (4.2)</td>
<td>46</td>
<td>0.094</td>
</tr>
<tr>
<td>Constructional Praxis (total No. correct)</td>
<td>8.9 (1.7)</td>
<td>8.8 (1.7)</td>
<td>57</td>
<td>0.599</td>
</tr>
<tr>
<td>Boston Naming Test (total No. correct)</td>
<td>14.6 (0.7)</td>
<td>14.4 (1.0)</td>
<td>47</td>
<td>0.215</td>
</tr>
<tr>
<td>Verbal Fluency (total No. correct)</td>
<td>19.0 (5.0)</td>
<td>18.8 (3.9)</td>
<td>48</td>
<td>0.699</td>
</tr>
</tbody>
</table>

*The sample size for nonparticipants having missing values of one or more variables of interest.
<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Outcome Variable</th>
<th>Covariate</th>
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<tbody>
<tr>
<td></td>
<td>Patella Lead</td>
<td>Blood Lead</td>
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<tr>
<td>Tibia lead</td>
<td>0.728*</td>
<td>0.438*</td>
</tr>
<tr>
<td>Patella lead</td>
<td>0.557*</td>
<td>-0.099</td>
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<tr>
<td>Continuous Performance (CP)</td>
<td>0.182†</td>
<td>-0.197†</td>
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<td>(latency-test trials)</td>
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<tr>
<td>Pattern Comparison (PCL)</td>
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<tr>
<td>Pattern Comparison (PCC)</td>
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<tr>
<td>Pattern Memory (PML)</td>
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<td>Pattern Memory (PMC)</td>
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<tr>
<td>Digit Span Backward (DSB)</td>
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<tr>
<td>Vocabulary (Vocab)</td>
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<td>Word List Memory (WLM)</td>
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<td>Constructional Praxis (CPRAX)</td>
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<tr>
<td>Boston Naming Test (BNT)</td>
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<td>Verbal Fluency (VF)</td>
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*p p < 0.01.
†p ≤ 0.05.
observed for patella lead and tibia lead, although they did not consistently reach significance in the regression analyses.

The half-life of lead in the patella is only a few years, compared to a half-life of decades for lead in the tibia (49). In contrast, concentrations of lead in blood fluctuate according to ongoing environmental lead exposure and the mobilization of endogenous stores of lead in bone (52). It is interesting to note that lead in tibia, which changes at a slower rate, showed more significant relationships with cognitive test scores in the regression analyses than did lead in the patella, which changes more rapidly. Although we do not know when lead exposures may have occurred, our findings do suggest that current levels of lead in blood are significantly associated with several aspects of cognitive functioning in these aging men. It is possible that any effect of lead on cognition is ongoing, and directly dependent on circulating blood lead, regardless of whether

<table>
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<th>Table 3</th>
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<tr>
<td>Adjusted Regression Models of Cognitive Outcomes in Relation to Lead Biomarkers in the Normative Aging Study, 1993–1994*</td>
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<tr>
<td>Test (Construct Measured)</td>
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<tr>
<td>Continuous Performance (sustained attention) (ms)</td>
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<td>Pattern Comparison (perceptual speed) (s)</td>
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<td>Pattern Comparison (perceptual speed) (total No. correct)</td>
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<tr>
<td>Pattern Memory (immediate visual memory) (s)</td>
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<td>Pattern Memory (immediate visual memory) (total No. correct)</td>
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<td>Digit Span Backward (auditory working memory) (total No.)</td>
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<td>Vocabulary (verbal ability) (total No.)</td>
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<td>Word List Memory (immediate verbal memory) (total No.)</td>
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<tr>
<td>Constructional Praxis (spatial copying) (total No.)</td>
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<td>Boston Naming Test (verbal ability) (total No.)</td>
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<td>Verbal Fluency Test (verbal ability) (total No.)</td>
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*In each model, the lead variable being analysed is not controlled for other lead variables; however, each model is adjusted for age and education.
†Significant in multivariate model including all three lead measures.
circulating lead results from current exposure or from mobili-
zation of bone lead.

The results of our study regarding blood lead are consist-
tent with findings from other research, including the only
other study we know of in which low levels of lead in older
adults were assessed in relation to cognition. Muldoon et al.
(38) found that higher levels of blood lead were associated
with slower psychomotor speed and poorer memory in elderly
women with low levels of lead (mean = 4.8 µg/dl). Our find-
ing of a relationship between lead and speed of cognitive per-
formance is also strikingly similar to that of Stollery et al.
(55,56), who found that men with higher levels of blood lead
due to occupational exposure required more time to attain
the same level of accuracy on some cognitive tests that measured
both accuracy and speed of performance as did men with
lower levels of lead. In our study, higher levels of blood lead
were associated with slower correct decisions on the Pattern
Comparison and Pattern Memory Tests (although results only
reached statistical significant in the case of the Pattern Com-
parison Test), but not with overall accuracy (Fig. 1). At least
on these fairly simple tasks, which did not require reasoning
or other complex skills, participants were able to reach similar
accuracy levels with no sign of an effect of lead.

A comparison of our results with those of Stollery et al.
(55,56) also suggests the importance of a match between sub-
ject sample characteristics and the difficulty of cognitive tests.
The lead workers examined by Stollery et al. had substantially
higher lead levels (mean of 14.1 µg/dl for the group with the
lowest level of blood lead) than did our participants, and ex-
hibited slowing on tests requiring milliseconds for decisions.
In contrast, our participants, who had lower lead levels (mean
of 5.5 µg/dl), demonstrated slower processing speed in rela-
tion to lead level only on tests on which decisions required re-
sponses on the order of seconds. Thus, it appears that in per-
sons with relatively low lead levels, the effects of lead on
speed of performance may be most discernable on tasks that
require more than a simple response time.

Processing speed has been associated with performance on
a variety of cognitive tests (30). In particular, degree of recall
on some measures of memory may be associated with individ-
ual differences among participants in speed of processing and/
or with rate of presentation of stimuli (46,63). One possible
pathway, therefore, by which lead may affect some forms of
cognitive functioning is through speed of processing. That is,
if higher concentrations of lead are associated with slower re-
sponse speed, this effect on response speed can then influence
performance on tasks that depend on speed. Although we do
not test this hypothesis specifically in this article, we do note
that speed of processing as measured by the mean response
time for correct items on the Pattern Comparison Test was as-
sociated significantly with better performance on the Word List
Memory Test ($r = -0.34$, $p < 0.01$). Success on this latter test
may have been dependent, at least in part, on participants’ effi-
ciency in using the time available to learn words. In contrast,
any relative deficits in processing speed due to lead exposure
did not differentially affect accuracy on the Pattern Compa-
rison and Pattern Memory tests, in which participants did not
have time constraints. Further research is needed to determine
the specific mental processes, such as speed, through which
lead can affect performance on various cognitive tasks.

The mechanism of lead’s effects on the brain remains un-
clear. Although the phenomenon has not been well studied in
humans, histopathological studies in animals support a rela-
tively localized effect of lead in the hippocampus and the limbic
system (3,57). Memory disorders and other cognitive changes
have been demonstrated following lesions to these neuroana-
tomical loci (36). Plausible neurological mechanisms by which
lead may exert its effects more generally on cognitive function
may include electrical deactivation of synapses, alteration of
neurotransmitters, and semipermanent changes in cell structure
or chemistry via protein synthesis. Whether and to what extent
such changes might affect cognition remains to be addressed.

There are limitations of this investigation that should be
mentioned. First, although our analyses controlled age and
education, cognition is determined by many factors. As in any
epidemiologic study, unknown confounders (including un-
measured variables) may explain the relation of lead to cogni-
tive function. Second, the error associated with the bone lead

![FIG. 1. Mean (95% CI) numbers correct (solid bars) and response times (open bars) for correct decisions, adjusted for age, on Pattern
Comparison and Pattern Memory Tests by quartiles of blood lead concentration (mean blood lead concentrations: Q1 = 1.4, Q2 = 3.5, Q3 =
5.4, Q4 = 9.8).](image)
measurements is large in comparison to the blood lead measurements, and probably contributed to a lesser ability to achieve conventional levels of statistical significance. Third, larger numbers of participants with higher lead levels may be required to find some associations and to reduce the probability of Type II error. The possibility of Type II error should be considered particularly in regard to the bone lead measures, which showed relations with cognitive outcomes consistently similar to those for blood lead, although associations did not often reach statistical significance.

We report that low levels of lead are associated with various cognitive abilities, including speed, verbal memory, language, and spatial copying in older community-dwelling men. Our results suggest that circulating lead in blood is a stronger indicator of performance on certain cognitive tests than is accumulated lead in bone. Further research, using longitudinal data from the NAS, will focus on the relation of the different biological markers of lead dose to the presence and rate of changes in cognitive function in aging men.

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