HIGH LIGHT
CME

Environmental lead exposure and cognitive function in community-dwelling older adults

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Abstract—*Objective:* To determine if long-term exposure to high levels of lead in the environment is associated with decrements in cognitive ability in older Americans. *Methods:* We completed a cross-sectional analysis using multiple linear regression to evaluate associations of recent (in blood) and cumulative (in tibia) lead dose with cognitive function in 991 sociodemographically diverse, community-dwelling adults, aged 50 to 70 years, randomly selected from 65 contiguous neighborhoods in Baltimore, MD. Tibia lead was measured with ^{109}Cd induced K-shell X-ray fluorescence. Seven summary measures of cognitive function were created based on standard tests in these domains: language, processing speed, eye-hand coordination, executive functioning, verbal memory and learning, visual memory, and visuoconstruction. *Results:* The mean (SD) blood lead level was 3.5 (2.2) μg/dL and tibia lead level was 18.7 (11.2) μg/g. Higher tibia lead levels were consistently associated with worse cognitive function in all seven domains after adjusting for age, sex, *APOE*-ε4, and testing technician (six domains $p \leq 0.01$, one domain $p \leq 0.05$). Blood lead was not associated with any cognitive domain. Associations with tibia lead were attenuated after adjustment for years of education, wealth, and race/ethnicity. *Conclusions:* Independent of recent lead dose, retained cumulative dose resulting from previous environmental exposures may have persistent effects on cognitive function. A portion of age-related decrements in cognitive function in this population may be associated with earlier lead exposure.

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Lead is found in measurable levels in all individuals.[1-3] It was extensively used in industrial, commercial, and residential products until a series of measures eliminated it from these uses beginning in the 1970s. Population-based studies in the 1970s documented average population blood lead levels exceeding 15 to 20 μg/dL[1-3]; this past widespread use has led to lifetime cumulative doses in most older Americans, who are now entering a period of life when age-related decline in cognitive function is prevalent. While it is not known whether early- and mid-life exposure to lead contributes to age-related loss of cognitive ability, the current generation of adults entering late life offers an opportunity to address this question.

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Lead accumulates in bone, with clearance half-times of approximately two to three decades from cortical bone (e.g., tibia),[4,5] where it can be measured using X-ray fluorescence.[6,7] It can contribute to blood lead levels, although the latter are primarily influenced by new external exposure.[8,9] Blood lead is the best available estimate of recent dose, while tibia lead is an estimate of lifetime retained cumulative dose.

Occupational studies have documented that lead adversely affects cognitive test scores as a function of recent and cumulative dose,[10-15] although controversy

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remains.[16] One study of older adults has examined associations of environmental lead exposure with cognitive performance,[17,18] but no studies have evaluated a diverse population-based study of adults. We investigated associations of blood lead and tibia lead with cognitive function in a population-based, random sample of urban-dwelling adults with diverse sociodemographic characteristics. If lead is associated with lower performance, this may suggest possible treatment and prevention options at the population level.

Methods. *Study population and design.* The Baltimore Memory Study is a multilevel longitudinal cohort study of urban-dwelling persons aged 50 to 70 years. The study design, recruitment, and sample characteristics have been previously described.[19-21] Briefly, households with telephone numbers located in 65 contiguous neighborhoods of Baltimore City were randomly selected and 18,826 were contacted to assess eligibility and interest in the study. Neighborhoods were selected to offer variation by race/ethnicity and socioeconomic status. Persons who had lived in Baltimore for at least 5 years and were 50 to 70 years of age were eligible. Among the 2,351 randomly chosen residents meeting these criteria, 1,140 (48.5%) were subsequently enrolled in the study. Of the 1,140 participants, 11 were of Hispanic or Latino ethnicity. A total of 1,033 (90.6%) subjects completed a second study visit approximately 14 months later, at which time tibia lead levels were obtained. All subjects provided written informed consent and were paid $50 for their time and effort. The study was approved by the Committee for Human Research at the Johns Hopkins Bloomberg School of Public Health.

Data collection. Data collection has been previously described.[19-21] All subjects completed baseline testing in this order: cognitive testing, blood pressure, height, weight, urine collection, structured interview, and venipuncture. The cognitive battery included 20 tests and required approximately 90 minutes to complete. It was assembled to assess a broad range of cognitive domains, to provide multiple measures of each cognitive domain, and to minimize differential item bias by race/ethnicity or socioeconomic status.[19-21] The structured interview consisted of self-reported information on race/ethnicity, age, sex, educational attainment, medications, household income, and household assets. Household wealth was defined as the sum of household income and household assets. Race/ethnicity was assessed to ensure representativeness of the population, and because race/ethnicity has been consistently associated with both lead dose[22,23] and cognitive performance in non-demented elderly.[20,24,25] The race/ethnicity categories were African American, African American-mixed, white (reference group), and other, which consisted of Native Americans, Asians, and four individuals who refused or were missing data on race/ethnicity. The methods used in deriving socioeconomic status measures (for education, income, and assets) have been previously described.[20]

Cognitive test scores were combined into domain summary scores before analysis (see below). General nonverbal intelligence, or crystallized intelligence, is thought to remain constant over the life course.[26] Thus, the Raven's Colored Progressive Matrices, a test of nonverbal reasoning that is commonly used as a surrogate for general cognitive ability,[27] was used to assess whether lifetime lead dose was associated with decrements in a test thought to be relatively stable over the life course.

Measurement of lead dose and APOE genotype. A phlebotomist obtained a blood sample, which was stored at –20 °C and then later transferred to –70 °C until lead measurement. Blood lead was measured from whole blood by anodic stripping voltammetry at the laboratories of the Kennedy Krieger Institute in Baltimore.[28] As an index of reliability, coefficients of variability (CV) for 5.9 μg/dL of lead were obtained, yielding values of 11% (intraday CV) and 7% (interday CV). The limit of detection was 1 μg/dL. The Malaria Institute laboratory at the Johns Hopkins Bloomberg School of Public Health performed the *APOE* genotyping, with methods described previously.[19] Tibia lead was measured at the second study visit by ^{109}Cd-induced K-shell X-ray fluorescence (XRF) using a 30-minute measurement of the mid-tibia shaft. XRF provides a measure of the average lead content in micrograms of lead per gram of bone mineral (hereafter μg/g). The technique has been validated and is highly reliable.[7,29] Blood lead was obtained at visit 1 for 1,120 (1,120/1,140 = 98.2%) individuals and tibia lead was measured during visit 2 for 1,010 people (1,010/1,033 = 97.8%).

Statistical analysis. The primary goal of the analysis was to compare associations of blood and tibia lead levels with cognitive test performance within seven domains using first visit data (except for tibia lead). Because of the long half-life (up to 30 years) of lead in tibia, levels measured at visit 2 were assumed to be valid estimates of levels at visit 1. The analysis included only participants who had both blood and tibia lead measurements and complete information on regression model covariates (n = 991). For the analysis, the three highest (148, 90.1, 85.4 μg/g) and two lowest negative values for tibia lead (–32.3, –32 μg/g) were excluded due to undue influence (greater than ± 4 SD from the mean). One subject had a blood lead level of 27.3 μg/dL that was 10 SD above the mean, so this was also excluded from the analysis. The final models thus included 985 subjects. All analyses were conducted using STATA version 8.0 software (StataCorp, College Station, TX).

The 20 cognitive test scores were collapsed into seven cognitive domain scores before analysis to minimize multiple comparisons and improve the measurement properties of the test scores for cognitive outcomes. All cognitive tests were z-transformed, and then averaged within domain to derive summary scores for each domain. Tests were grouped based on neuropsychological theory and supported by examination of correlation matrices (Spearman and Pearson) and results of single linkage cluster analysis (data not shown). The domains included language (consisting of Boston naming test, letter fluency, and category fluency), processing speed (simple reaction time), eye-hand coordination (Purdue pegboard dominant hand, non-dominant hand, and both hands, and trail-making test A), executive functioning (consisting of the mean of three z-transformed difference scores: Purdue pegboard assembly minus both hands, Stroop C form minus A form, and trail-making test B minus A), verbal memory and learning (Rey auditory verbal learning test immediate recall, delayed recall, and recognition), visual memory (Rey complex figure delayed recall and symbol digit), and visuoconstruction (Rey complex figure copy). All seven domain scores were standardized for direction so that a negative regression coefficient indicated worse performance with increasing lead levels.

Additional variables were included in the base regression model (Model I) if they were independently associated with the outcomes or if they substantively influenced the relation of lead with the outcome. The base model included age, sex, testing technician (four technicians), and presence of at least one *APOE-ε4* allele (ε2ε4, ε3ε4, ε4ε4 vs no ε4 allele). Subsequent models were motivated by specific a priori hypotheses we wished to test about whether the main effect of lead was independent of other factors. To this base model we added years of education (Model II), race/ethnicity (Model III), and finally, years of education, race/ethnicity, and household wealth (ln-transformed), together (Model IV). The associations of tibia and blood lead were modeled separately for all models, except Model Ia, in which the two were included together to determine whether blood lead masked any tibia lead associations (or vice versa). To evaluate non-linearity, quadratic terms were included for tibia lead and blood lead. Non-linearity was not observed so quadratic terms were not included in the final models. All models were examined for normality, influence of outliers, multi-colinearity, and heteroscedasticity using added variable plots, distribution of residuals, and variance inflation factors. The added variable plots revealed that one domain in particular, processing speed, had 10 extreme residual values (more negative than –4); these points were thus removed and linear regressions repeated.

Results. *Description of study subjects.* The 985 study subjects were 34.1% male, 40.1% African American, and had a mean (SD) age of 59.4 (6.0) years (table 1). The individuals in whom blood lead measurements were not obtained were more likely to be female ($p = 0.03$). Individuals in whom tibia lead measurements were not obtained were less educated ($p = 0.01$) and more likely to be African

Table 1 *Characteristics of participants in the Baltimore Memory Study (n = 985, with full information)*

Variable name	Total sample, n = 985	African American, n = 395	White and other, n = 590	*p* Value*
Age, y, mean (SD)	59.39 (5.96)	59.77 (6.24)	59.14 (5.75)	0.11
Female sex, n (%)	649 (65.89)	284 (71.90)	365 (61.86)	0.001
Education, y, mean (SD)	14.77 (3.90)	13.17 (3.09)	15.83 (4.03)	<0.001
Wealth, ln-transformed, mean (SD)	12.20 (1.09)	11.68 (0.88)	12.55 (1.08)	<0.001
Coloured Progressive Matrices score, mean (SD)	30.59 (4.71)	28.12 (5.08)	32.24 (3.62)	<0.001
APOE-ε4 no allele, n (%)	693 (70.36)	249 (63.04)	444 (75.25)	<0.001
One allele, n (%)	267 (27.11)	129 (32.66)	138 (23.39)	
Two alleles, n (%)	25 (2.54)	17 (4.30)	8 (1.36)	
Tibia lead level, μg/g, mean (SD)	18.72 (11.24)	21.62 (11.73)	16.78 (10.47)	<0.001
Blood lead level, μg/dL, mean (SD)	3.46 (2.23)	3.46 (2.31)	3.46 (2.18)	0.99
Cognitive domain z-scores,† mean (SD)				
Language	0.02 (0.83)	−0.49 (0.80)	0.35 (0.65)	<0.001
Processing speed	0.05 (0.94)	−0.25 (1.12)	0.25 (0.72)	<0.001
Eye-hand coordination	0.02 (0.76)	−0.27 (0.85)	0.21 (0.63)	<0.001
Executive functioning	0.04 (0.72)	−0.34 (0.71)	0.29 (0.60)	<0.001
Verbal memory and learning	0.03 (0.88)	−0.30 (0.96)	0.25 (0.75)	<0.001
Visual memory	0.03 (0.85)	−0.30 (0.78)	0.25 (0.82)	<0.001
Visuoconstruction	0.04 (0.99)	−0.46 (0.99)	0.37 (0.83)	<0.001

* *p* Values indicate whether variable distributions differ between African Americans and White and Other race/ethnicity groups, calculated by two sample *t* tests for continuous variables, and by χ^2 tests for categorical variables. Bartlett variance comparison test was used in the case of continuous variables.
† Domain z-scores evidenced slight departures from expected values (mean = 0, SD = 1) because z-transformation was performed using data from all 1,140 study subjects at visit 1.

American ($p = 0.02$). As expected, mean blood lead levels were low, but mean tibia lead levels were moderate to high (table 1). Tibia lead levels were significantly higher in African Americans vs whites. Blood and tibia lead were weakly correlated (Pearson and Spearman r values for the lead variables used in the analysis were both 0.14), suggesting that, as expected, current exposures were low but past cumulative exposures were moderate to high.

Associations of lead dose with cognitive function. After adjustment for covariates, blood lead was not consistently associated with any domain of cognitive function (table 2). In contrast, tibia lead was associated ($p \leq 0.05$) with worse performance in all domains in Model I (table 3 and figure E-1 on the *Neurology* Web site at www.neurology.org). Addition of either educational attainment or race/ethnicity alone to the base model attenuated the tibia lead coefficients. In Model IV, only one (visuoconstruction ability) of seven domain scores remained associated with tibia lead ($p \leq 0.10$). Adding blood lead to each of the models did not appreciably change any of the tibia lead associations (data shown only for Model Ia). Tibia lead, but not blood lead, was associated with worse performance on Colored Progressive Matrices ($p < 0.001$). There was no evidence of effect modification by race/ethnicity on the associations between tibia lead and cognitive function after inclusion of a cross-product term of race/ethnicity and tibia lead.

Magnitude of lead associations. To evaluate the magnitude of the lead associations, we compared these associations to those for age, using results from Model I (table 4). Across an interquartile range of tibia lead (11.9 to 24.8 μg/g), the association of tibia lead was between 22% to 60% of the association of an interquartile range of age (54.0 to 64.2 years) across the seven domains.

Discussion. In this population-based study of urban-dwelling adults with diversity by sex, race/

Table 2 *Change in cognitive domain scores per 1 μg/dL increase in blood lead: Baltimore Memory Study*

	Model I		Model Ia		Model II		Model III		Model IV	
Cognitive domain	β*	SE	β*	SE	β*	SE	β*	SE	β*	SE
Language	−0.0060	0.0118	0.0011	0.0119	−0.0064	0.0102	−0.0006	0.0100	−0.0019	0.0091
Processing speed	−0.0109	0.0109	−0.0075	0.0110	−0.0107	0.0107	−0.0088	0.0104	−0.0083	0.0103
Eye-hand coordination	−0.0110	0.0106	−0.0045	0.0107	−0.0113	0.0101	−0.0076	0.0100	−0.0076	0.0096
Executive functioning	−0.0143	0.0099	−0.0082	0.0100	−0.0144	0.0093	−0.0097	0.0089	−0.0101	0.0086
Verbal memory & learning	−0.0181	0.0124	−0.0118	0.0125	−0.0184	0.0117	−0.0139	0.0117	−0.0151	0.0114
Visual memory	−0.0137	0.0121	−0.0081	0.0122	−0.0139	0.0115	−0.0101	0.0114	−0.0107	0.0112
Visuoconstruction	−0.0191	0.0138	−0.0090	0.0138	−0.0195	0.0127	−0.0132	0.0125	−0.0143	0.0120

Model I: Adjusting for age, sex, technician (categorical), presence of *APOE*-ε4 allele (ε2ε4, ε3ε4, ε4ε4 vs no ε4 allele). Model Ia: Model I + tibia lead (continuous). Model II: Model I + years of education (continuous). Model III: Model I + race/ethnicity (four categories: white as reference). Model IV: Model I + years of education + race/ethnicity + wealth (ln-transformed).

* All coefficients were standardized so that negative values always indicate worse functioning.

Table 3 *Change in cognitive domain score per 1 μg/g increase in tibia lead level: Baltimore Memory Study*

	Linear regression models									
	Model I		Model Ia		Model II		Model III		Model IV	
Cognitive domain	β*	SE	β*	SE	β*	SE	β*	SE	β*	SE
Language	−0.0083	0.0023§	−0.0083	0.0023§	−0.0046	0.0020‡	−0.0007	0.0020	0.0006	0.0018
Processing speed	−0.0042	0.0021‡	−0.0040	0.0022†	−0.0030	0.0021	0.0003	0.0021	0.0004	0.0021
Eye-hand coordination	−0.0079	0.0020§	−0.0077	0.0021§	−0.0060	0.0020§	−0.0037	0.0020†	−0.0026	0.0019
Executive functioning	−0.0075	0.0019§	−0.0072	0.0019§	−0.0053	0.0018§	−0.0022	0.0018	−0.0014	0.0017
Verbal memory & learning	−0.0078	0.0024§	−0.0074	0.0024§	−0.0054	0.0023‡	−0.0027	0.0023	−0.0021	0.0023
Visual memory	−0.0067	0.0023§	−0.0064	0.0024§	−0.0046	0.0023‡	−0.0019	0.0023	−0.0012	0.0022
Visuoconstruction	−0.0122	0.0027§	−0.0119	0.0027§	−0.0091	0.0025§	−0.0054	0.0025‡	−0.0044	0.0024†

Model I: Adjusting for age, sex, technician (categorical), presence of *APOE*-ε4 allele (ε2ε4, ε3ε4, ε4ε4 vs no ε4 allele). Model Ia: Model I + blood lead (continuous). Model II: Model I + years of education (continuous). Model III: Model I + race/ethnicity (four categories: white as reference). Model IV: Model I + years of education + race/ethnicity + wealth (ln-transformed).

* All coefficients were standardized so that negative values always indicate worse functioning.
† $0.05 < p \leq 0.10$; ‡ $0.01 < p \leq 0.05$; § $p \leq 0.01$.

ethnicity, and socioeconomic status, we evaluated associations of blood lead and tibia lead with cognitive function. An extensive neuropsychological test battery assessed cognitive function, and study subjects were randomly selected from an urban population of adults aged 50 to 70 years, comprised of both African Americans and whites and with a range of socioeconomic status. Higher tibia lead was significantly associated with worse cognitive function in all domains, but blood lead was not so associated. The magnitudes of the tibia lead associations were moderate to large; an increase of one interquartile range of tibia lead was equivalent to 2.2 to 6.1 more years of age across all domains, and the average tibia lead effect was 36% of the age effect. While comparison of these magnitudes must be interpreted with caution, given the cross-sectional design of the study and the limited age range of study subjects, the findings suggest that, in this population, a proportion of what has been termed normal age-related decrements in cognitive function may be attributable to neurotoxicants such as lead.

Table 4 *Magnitude of associations comparing one interquartile range (IQR)§ in lead level to one IQR for age (from Model I)**

	Age†	Tibia lead‡	Equivalent years in age per IQR of tibia lead
Language			
β	−0.352	−0.108	3.1
% of age effect	100%	30.7%	
Processing speed			
β	−0.092	−0.055	6.1
% of age effect	100%	59.8%	
Eye-hand coordination			
β	−0.373	−0.102	2.8
% of age effect	100%	27.3%	
Executive functioning			
β	−0.364	−0.098	2.7
% of age effect	100%	26.9%	
Verbal memory & learning			
β	−0.271	−0.102	3.8
% of age effect	100%	37.6%	
Visual memory			
β	−0.396	−0.087	2.2
% of age effect	100%	22.0%	
Visuoconstruction			
β	−0.335	−0.159	4.8
% of age effect	100%	47.5%	

* No associations were observed between blood lead and cognitive domain scores after adjusting for age, sex, testing technician, *APOE*-ε4 allele.
† Adjusted for sex, testing technician, tibia lead level, *APOE*-ε4 allele (ε2ε4, ε3ε4, ε4ε4 vs no ε4 allele).
‡ Adjusted for age, sex, testing technician, *APOE*-ε4 allele (ε2ε4, ε3ε4, ε4ε4 vs no ε4 allele).
§ The IQR for age was 10.2 years and for tibia lead was 13 μg/g.

Study participants consisted of urban-dwelling 50- to 70-year-old adults with currently low levels of environmental lead exposure, and in whom peak lead exposure likely occurred 30 years prior (before the phase-out of lead in commercial products).[30] We interpret this to mean that lifetime cumulative lead dose, not recent dose, was associated with worse cognitive function in our study subjects.

We believe the findings to be biologically plausible. While the majority of early studies evaluated the mechanism of lead neurotoxicity in young animals after early life exposure, a growing literature has begun to elucidate the mechanisms underlying the effect of lead on the CNS in adult animals. Lead alters the permeability of the mature blood–brain barrier,[31] accumulates in astroglia,[32] which are essential to maintenance of the neuronal environment, especially regarding the excitotoxic neurotransmitter glutamate, and affects glutamate homeostasis.[32,33] Adult lead exposure can produce apoptotic cell death in retinal and hippocampal cells and may interfere with long-term potentiation.[34,35] Lead may alter energy metabolism in mitochondria and synaptosomes,[36] and can interfere with several calcium-

dependent processes, including the activity of protein kinase C.[37,38] Recent evidence also suggests that lead accumulates in myelin, inhibits integral enzymes there, and may contribute to ultrastructural changes, or other changes in myelin.[39] This last finding is particularly relevant given increasing interest in the myelin hypothesis of neurodegenerative diseases.[40] Recent human studies have also supported the biologic plausibility in reporting that 1) higher tibia lead was associated with increased prevalence and severity of white matter lesions, and with smaller volumes of large and small brain structures[41]; 2) the *APOE*-ε4 allele increased cognitive deficits associated with tibia lead[42]; and 3) higher blood lead levels were associated with higher homocysteine levels, which have been associated with cognitive deficits in several studies.[19,43]

In regression models adjusting for age, sex, testing technician, and *APOE*-ε4 (Model I, table 3), strong and consistent associations of tibia lead with cognitive function across multiple domains were observed. Adjustment for race/ethnicity, educational attainment, and wealth in Models II through IV substantially attenuated these associations. To the extent that race/ethnicity, education, and household wealth are potential confounders, adjusting for these factors as we did would yield better estimates of the true association between lead and cognitive function. It is possible that higher tibia lead levels are associated with lower secondary school quality or innate intellectual ability, and that the association of tibia lead with lower cognitive function is explained by its association with these other factors. A large literature discusses the complexities and controversies of adjustment for race/ethnicity in studies of this type.[44] We examined associations with and without such control and the findings were less robust when race/ethnicity was included. Adjustment for race/ethnicity requires considerable evidence and robust causal knowledge,[45] and we do not believe its inclusion in these models is appropriate. Finally, it is also possible that unmeasured confounders could account for the observed associations.

However, there are at least three possible underlying causal structures under which adjusted associations would misrepresent the relevant associations with tibia lead. We posit that[23] adjusting for educational attainment, race/ethnicity, and socioeconomic status would lead to underestimation of the relevant health effect of tibia lead if 1) lead exposure in early life caused lower educational or occupational achievement,[46,47] due, at least in part, to an effect of lead on IQ,[48,49] and that educational attainment may influence likelihood of exposure to lead[48] (reciprocal effects model); 2) race/ethnicity was more correlated with lifetime lead dose than was tibia lead, or if there was differential tibia lead measurement error by race/ethnicity[50] (measurement error model); or 3) there were unmeasured effect modifiers (e.g., cardiovascular health) that differed by race/ethnicity that were not included in the models (unmeasured effect modification model). There is strong existing evidence in favor of each of these causal structures.

Statistical adjustment for educational attainment would be appropriate if current tibia lead levels reflected only later life exposures and the observed associations between tibia lead and cognitive function were due to only these later life exposures. However, it is also known that early life lead exposure influences full scale IQ, behavioral, and neuropsychological outcomes,[46,51] which may ultimately affect educational outcomes. Thus, the association between tibia lead and cognitive function would be underestimated if the reciprocal effects between lead dose and education were not appropriately accounted for.

Population-based studies indicate that our study subjects had early life lead exposures.[1-3] Given the patterns of environmental lead exposure over the past 50 to 70 years and the clearance of lead from tibia over time, we would conclude that a proportion of the lead in tibia measured in this study sample of older adults would have been deposited in the first decade of life, the majority in the second to fourth decades of life, and a smaller proportion from more recent decades, after the elimination of lead from commercial products. Although tibia lead levels reflect mostly late life lead exposure, we observed that performance on a measure of nonverbal reasoning, Colored Progressive Matrices, was worse ($p < 0.001$) with higher tibia lead levels. Colored Progressive Matrices is an untimed test of general nonverbal reasoning. The test does not depend on language ability, which may be altered by exposure to neurotoxicants like lead,[13] and is not as culturally biased as most other surrogate tests of general cognitive capacity.[52] Therefore this association provides evidence that, even in our relatively older study subjects, early life lead exposure may have influenced this surrogate measure of IQ. Overall, these associations of current tibia lead levels with cognitive function and Colored Progressive Matrices suggest that both early life and adult lead exposures are likely to have contributed to the observed cognitive deficits.

Blood lead levels in study participants did not differ by race/ethnicity, however, mean tibia lead levels were significantly higher in African Americans. The differences in tibia lead levels by race/ethnicity likely represent the long-term higher environmental lead exposures sustained by African Americans in this country, but they could also be physiologic in origin. During late-life aging, African Americans have higher average bone mineral densities and slower declines in bone mineral density than non-African Americans, especially among perimenopausal women.[53] The measurement error model proposes that tibia lead may not be a complete surrogate for cumulative lead dose because of individual variation in remote exposures, bone demineralization rates, and clearance of lead from bone. Tibia lead is measured as μg of lead per gram of bone mineral. If bone mineral is lost more quickly than lead in bone, bone lead concentration may appear to be falsely higher than

true lifetime cumulative dose. If bone mineral were lost more slowly than lead, bone lead concentrations would be falsely lower than the true lifetime cumulative dose. Adjustment for race/ethnicity in regression models would consequently lead to an underestimation of the direct association between cumulative lead dose and cognitive function if race/ethnicity served as a better surrogate for lifetime cumulative dose than tibia lead. This problem would be exacerbated if there was differential measurement error by race/ethnicity.

It is also likely that there are unmeasured common causes that are more prominent in one racial/ethnic subgroup than the other. These unmeasured common causes may modify the association between lead exposure and cognitive function (unmeasured effect modification). Numerous studies have reported the disparities in cognitive health by race/ethnicity, with older African Americans performing worse on cognitive tests than older white adults.[20,25] However, this is likely due to a host of risk factors for which race/ethnicity serves as a proxy. For example, compared to non-African Americans, African Americans in the United States are more likely to experience socioeconomic discrepancies in educational quality, and the extent of educational attainment,[54-56] and have higher rates of diabetes, heart disease, hypertension, and other factors that accumulate over the life course to threaten brain integrity.[57-59]

The cognitive tests used in this study were chosen because of their purported variation by race/ethnicity and socioeconomic status.[20] However, differential measurement of cognitive function by race/ethnicity may still occur given that most tests were initially developed for white populations. Differential item functioning by race/ethnicity resulting from either sociocultural insensitivity or discrepancies in socioeconomic factors, health conditions, or health behaviors could also partially account for the disparity in cognitive function separate from inherent ability.[60,61]

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