Gender and Race/Ethnicity Differences in Lead Dose Biomarkers

Keson Theppeang, MHS, Thomas A. Glass, PhD, Karen Bandeen-Roche, PhD, Andrew C. Todd, PhD, Charles A. Rohde, PhD, and Brian S. Schwartz, MD

Objectives. We sought to identify predictors of lead concentrations in the blood, tibias, and patellae of older adults and to describe differences by gender, race/ethnicity, and other factors that can influence lead toxicokinetics and, thus modify health effects.

Methods. Participants aged 50 to 70 years (N = 1140) were randomly identified from selected neighborhoods in Baltimore, Maryland. We measured lead concentrations by anodic stripping voltammetry (in blood) and ^{109}Cd-induced K-shell x-ray fluorescence (in bone). We used multiple linear regression to identify predictors of lead concentrations.

Results. Mean (SD) lead concentrations in blood, tibias, and patellae were 3.5 (2.4) μg/dL, 18.9 (12.5) μg/g, and 6.8 (18.1) μg/g, respectively. Tibia concentrations were 29% higher in African Americans than in Whites ($P < .01$). We observed effect modification by race/ethnicity on the association of gender and physical activity to blood lead concentrations and by gender on the association of age to tibia lead concentrations. Patella lead concentrations differed by gender; apolipoprotein E genotype modified this relation.

Conclusions. African Americans evidenced a prominent disparity in lifetime lead dose. Women may be at higher risk of release of lead from bone and consequent health effects because of increased bone demineralization with aging. (*Am J Public Health.* 2008;98:1248–1255. doi:10.2105/AJPH.2007.118505)

Lead was widely distributed in the environment from the beginning of the past century until it was removed from most commercial uses in the 1980s.[1,2] Because of lead's widespread use, average blood lead concentrations among persons in the general population were estimated to be higher than 20 μg/dL in the 1960s[3] and 13 to 15 μg/dL in the late 1970s.[2] In blood, lead has a short clearance half-time of approximately 30 days but collects in bone; in the tibia, the clearance half-time is almost 3 decades.[4] Thus, past lead exposure can influence population health in several ways: through its persistence in the environment, persistent or progressive health effects from remote exposures,[5] or accumulation in, and later release from, bone in older adults who were alive during the period of peak population exposure.

Currently, most American adults have low blood lead concentrations,[2] which represent integrated internal (release from bone) and external exposures over an average of the prior 120 days. However, older adults can have moderate to high bone lead concentrations.[6] Tibia lead, with its long clearance half-time, is an estimate of cumulative dose from past exposures.[6] The trabecular bone tissue in the patella is more biologically active and, with a clearance half-time of 3 to 5 years, is an estimate of the bioavailable bone lead pool.[7,8] Because the metabolism of lead in bone is similar to that of calcium,[9] bone lead can serve as an endogenous source of internal exposure,[10–12] particularly associated with accelerated demineralization in osteoporosis or aging,[11,13–15] resulting in subsequent risk of deposition in critical target organs.[16]

To date, studies of bone lead concentrations have focused on populations in Boston, Massachusetts, or Mexico City, Mexico, with no diversity within studies by race/ethnicity, gender, or socioeconomic status (SES).[6,17–27] Although other studies have documented differences in blood lead concentrations by race/ethnicity and SES,[2,28,29] these studies did not simultaneously measure bone lead concentrations. No population-based studies have compared the bone lead concentrations of large numbers of African Americans and Whites, and no studies have included participants across the full spectrum of SES. Understanding differences in bone lead concentrations in blood, tibias, and patellae across sociodemographic groups may contribute to an explanation of persistent and widening health disparities.[28,30–32] This could lead to interventions to prevent or lessen the health risks associated with lead in late life.

We examined lead concentrations and from our analysis determined predictors of blood, tibia, and patella lead concentrations in a population-based study of community-dwelling urban residents aged 50 to 70 years with diversity by gender, race/ethnicity, and SES.

METHODS

Study Population and Design

The study design, population, and assessment methods for the Baltimore Memory Study (BMS) have been previously reported.[33] In brief, the BMS is a prospective study of 1140 urban residents, aged 50 to 70 years. Participants were selected by stratified random sampling from 65 contiguous neighborhoods in central and north Baltimore, Maryland. All participants were scheduled for 3 visits at approximately 14-month intervals; 1022 (89.6%) completed the second visit, and 943 (82.7%) completed the third visit. Of the 197 who did not return for the third visit, 101 (9% of those enrolled) refused, 23 (2%) were too ill, 21 (2%) were deceased, 38 (3%) were lost to follow-up, and 14 (1%) had moved out of state. There was no evidence of selective dropout by age, gender, race/ethnicity, education, or wealth (all $P > .05$ by χ^2 or analysis of variance). All participants provided

written informed consent and were paid $50 at each visit.

Data Collection

Data were collected at the study clinic in the following order: neurobehavioral testing, blood pressure, height, weight, spot urine collection, structured interview, and a 10-mL blood specimen by venipuncture. We utilized data from all 3 visits in a cross-sectional analysis. Demographics, medications, tobacco and alcohol histories, blood lead concentrations, and genotypes were from the first visit; tibia lead concentrations, dietary intake, and physical activity were from the second visit; and patella lead concentrations were from the third visit.

Laboratory Methods

Blood lead concentrations were measured with anodic stripping voltammetry (ESA Laboratories, Chelmsford, Massachusetts).[33] We used ^{109}Cd-induced K-shell x-ray fluorescence to measure tibia and patella lead concentrations in units of micrograms of lead per gram of bone mineral (μg/g), at the midtibia shaft and left-center patella.[34,35] Because of a growing literature that suggests the toxicokinetics of lead may be modified by genetic polymorphisms,[36,37] we also evaluated associations with 2 genes thought relevant to deposition or release of lead or calcium from bone: apolipoprotein E, *APOE,* and vitamin D receptor, *VDR* (by using 2 restriction enzymes, *Bsm*I and *Fok*I).[38–41] Genotyping was performed in the laboratory of the Malaria Institute in the Bloomberg School of Public Health by standard methods.[38,42]

Diet and Physical Activity

We assessed dietary intake with the Block Dietary Questionnaire (Block 98.2, Berkeley Nutrition Services, Berkeley, California), and we calculated nutritional intake estimates based on the National Health and Nutrition Examination Survey III and US Department of Agriculture food intake databases by using DIETSYS software (National Cancer Institute, Bethesda). We used the Yale Physical Activity Survey[43] to assess physical activity in 5 categories (work, yard work, caretaking, exercise, recreation) as frequency per week, duration of activity per time, and seasonal variation. We then derived standard metrics (8 indices and 2 additional measures), including an energy expenditure summary index, total time summary index, and vigorous-activity index score.

Statistical Analysis

The primary goals of this cross-sectional analysis were to (1) describe differences in lead concentrations in blood, tibia, and patella by gender, race/ethnicity, and SES; (2) evaluate correlates of the 3 lead concentration biomarkers (lead in blood, tibia, and patella) with linear regression; and (3) examine the effect modification of these relations by important potential moderators, such as age, gender, race/ethnicity, physical activity, dietary intake, and genetic polymorphisms. By comparing and contrasting associations with lead concentrations in these 3 pools with different biology and kinetics, we sought to understand the biology underlying gender, race/ethnicity, and SES differences.

Because the distribution of results was skewed in the sample, we natural logarithm (ln)–transformed blood lead concentrations to reflect a more normal distribution before we regressed them on the covariates. The adequacy of the ln-transformation was examined with residual distributions. To facilitate the interpretation of results, we present the back-transformed parameter estimates from the analysis of the ln-transformed sample distributions. The resulting parameter estimates estimated ratios of the median sample distributions across predictor-level units.

Measurement of bone lead concentrations with ^{109}Cd-induced K-shell x-ray fluorescence can produce negative point estimates when the true bone lead concentration is close to zero.[44] Negative values were particularly common for patella lead concentrations; 30.9% of the samples had values that were less than or equal to zero. We thus used Tobit regression[45,46] with left truncation at 0 μg/g to model tibia and patella lead concentrations. In brief, Tobit is used to model data whose distribution is limited compared with the normal distribution, for example, distributions that are truncated or censored. In the Tobit model, which uses maximum likelihood estimation, it is assumed that there is an underlying latent variable of interest generated by the linear regression model with an error term that is normally distributed, $y_i^* = X_i\beta + \varepsilon_i$, where $\varepsilon_i \sim N(0,\sigma^2)$, but for which we have only observed $y_i = max(0, y_i^*)$.

We used Stata version 8 statistical software (Stata Corp, College Station, Texas) to separately model blood, tibia, and patella lead concentrations. We used multiple linear regression to adjust estimates for potential confounding by conditioning on observed covariates including body mass index (BMI; weight in kilograms divided by height in meters squared), tobacco and alcohol consumption, oral corticosteroid use, postmenopausal hormone use, other relevant medication use, and lifestyle and other risk factors for bone mineral loss (e.g., specific medical conditions, dietary history, physical activity, age, gender, race/ethnicity). Variables were retained in the final models if they were (1) known to be important based on prior studies, (2) significant predictors ($P<.05$) of lead biomarkers, (3) a confounder (based on a 10% change in regression coefficients), or (4) an effect modifier of the relations of interest. Formal tests of effect modification were performed by comparing improvement in model fit in nested models with and without appropriate cross-product terms.

We used generalized estimating equations to simultaneously model and directly compare predictors of tibia and patella lead concentrations in the same models while accounting for within-participant correlations of the measurements.[47,48] Bone lead concentrations were first z-transformed so that concentrations could be compared on the same scale. These models included an indicator variable for bone site and cross-product terms between this indicator variable and predictors of interest (e.g., age, gender, race/ethnicity). In these models, significant cross-products would indicate that the association of predictor variables with bone lead concentrations differed for tibias and patellae.

We used examination of distributions, residuals, partial residual plots, and variance inflation factors to evaluate the assumptions of linear regression and goodness of fit.[49] We also evaluated potential nonlinearity by inclusion of quadratic terms in the linear regression models (retained if $P<.05$).

RESULTS

Description of Study Participants

The 1140 study participants included 53.7% of White and 41.6% of African American race/ethnicity. Considering all races/ethnicities, study participants consisted of 391 (34.3%) men and 749 (65.7%) women. The mean (SD) blood, tibia, and patella lead concentrations were 3.5 (2.4) μg/dL, 18.9 (1.25) μg/g, and 6.8 (18.1) μg/g (with negative values as negative), respectively. The prevalence of the *APOE* ε4 allele was 30.2%. The prevalence of the *VDR bsm*I BB genotype and *fok*I ff genotype were 12.8% and 10.5%, respectively. There were differences in mean tibia lead concentrations and important covariates by race/ethnicity (Table 1, presenting African Americans and Whites only because of small numbers of participants of other races/ethnicities) and in mean blood and patella lead concentrations and important covariates by gender (Table 2).

Predictors of Blood Lead Concentrations

In adjusted analyses, on average, participants who were female, had higher BMI, had higher dietary vitamin D or calcium supplement intake, and had a higher Yale vigorous activity index had lower ln-transformed blood lead concentrations (Table 3, model 1). By contrast, current smokers, those with higher tibia lead concentrations, those who consumed alcoholic beverages in the past month, and those who had a higher Yale energy index had higher ln-transformed blood lead concentrations (Table 3, model 1). Patella lead concentrations were not associated with blood lead concentrations in adjusted models without ($P>.10$) or with ($P>.30$) tibia lead concentrations in the model. The median blood lead concentration was 41% lower for women than for men ($P<.01$), 0.7% higher for every 1-μg/g increase in tibia lead concentrations, 0.5% lower for every 1-unit increase in the Yale vigorous activity index, and 0.1% higher for each 100-kilocalorie per week increase in the Yale energy index.

We next examined effect modification by potential moderators of the relations between ln-transformed blood lead concentrations and selected covariates (using model 1; Table 3). The relations between gender and blood lead concentrations were modified by the Yale vigorous activity index and race/ethnicity (Table 3, models 2 and 3, respectively). The male–female differences in adjusted median blood lead concentrations were different for Whites and African Americans ($P=.04$), with magnitudes of gender differences of 49% and 27%, respectively (derived from combining parameter estimates from model 3). There was also a gender difference in the relation of the Yale vigorous activity index with blood lead concentrations ($P=.02$); median blood lead concentrations declined 0.06% per unit increase in the index for men, but declined 0.8% per unit increase in women. Finally, hormone replacement therapy use in women was associated with 37% lower blood lead concentrations ($P<.01$; Table 3, model 4).

Predictors of Tibia Lead Concentrations

In adjusted analyses, on average, participants who were older, African American and had a higher Yale energy index, higher daily dietary vitamin D intake, and lower daily dietary calcium intake had higher tibia lead concentrations (Table 4, model 1). The average adjusted tibia lead concentrations among

TABLE 1—Selected Characteristics and Variables by Race/Ethnicity: Baltimore Memory Study, Baltimore, MD, 2001–2005

Variables	African Americans (n = 474)	Whites (n = 612)	P[a]
Lead levels, mean (SD)			
Tibia, μg/g	21.8 (12.8)	16.7 (12.0)	<.01
Patella, μg/g	7.1 (17.7)	7.1 (16.6)	.46
Patella,[b] μg/g	15.9 (11.4)	14.6 (12.3)	.18
Blood, μg/dL	3.6 (2.3)	3.6 (2.4)	.69
Demographics			
Age, y, mean (SD)	59.6 (6.2)	59.0 (5.8)	.17
Women, no. (%)	339 (71.5)	368 (60.1)	<.01
Wealth,[c] $10 000, mean (SD)	10.8 (10.3)	65.9 (312.5)	<.01
Dietary intake			
Dietary vitamin D, 100 IU, mean (SD)[d]	1.3 (1.2)	1.6 (1.4)	<.01
Dietary calcium, 100 mg, mean (SD)[d]	5.8 (3.9)	7.3 (4.3)	<.01
Supplemental vitamin C use, no. (%)	228 (54.4)	383 (67.9)	<.01
Medical history and medications, no. (%)			
Self-reported diabetes	123 (26.0)	80 (13.1)	<.01
Oral corticosteroid medication use	8 (1.7)	10 (1.6)	.80
Physical activity, mean (SD)			
Yale energy index[e], 100 kcal/wk	91.2 (71.6)	72.7 (50.1)	<.01
Yale vigorous activity index score[f]	13.2 (16.0)	18.0 (16.1)	<.01
Genetic polymorphisms			
Apolipoprotein E ε4 allele, no. (%)	178 (37.6)	166 (25.0)	<.01
Vitamin D receptor *Bsm*I BB genotype, no. (%)	36 (7.7)	109 (16.4)	<.01
Vitamin D receptor *Fok*I ff genotype, no. (%)	20 (4.3)	99 (14.9)	<.01

[a]*P* values reflect evaluation of differences by race/ethnicity from *t* statistics for continuous variables or from the χ^2 test for binary and categorical variables.
[b]Included only participants who had patella lead concentrations greater than zero.
[c]Wealth was defined as the total dollar value of household assets plus total household income from visit 1.
[d]Daily intakes of dietary vitamin D and calcium were estimated on the basis of nutritional contents of vitamin D and calcium from consumption of a wide variety of food items over the past year including frequency, number of servings per ingestion, and the portion size.
[e]Time spent for each activity on the checklist was multiplied by an intensity (kcal/min) and was summed over all activities to create a total energy expenditure index for each participant.
[f]The frequency score was multiplied by the duration score to create a vigorous activity index score.

TABLE 2—Selected Participant Characteristics and Variables, by Gender: Baltimore Memory Study, Baltimore, MD, 2001–2005

Variables	Women (N = 749)	Men (N = 391)	P[a]
Lead concentration, mean (SD)			
Blood, μg/dL	3.1 (2.0)	4.4 (2.8)	<.01
Patella, μg/g	4.7 (18.7)	10.9 (16.0)	<.01
Patella,[b] μg/g	14.5 (11.3)	16.1 (13.0)	.09
Tibia, μg/g	19.4 (13.0)	18.0 (11.5)	.12
Dietary intake			
Dietary vitamin D, 100 IU, mean (SD)[c]	1.4 (1.4)	1.6 (1.4)	.08
Supplemental calcium use, no. (%)	433 (63.5)	172 (49.4)	<.01
Physical activity			
Yale energy index,[d] 100 kcal/wk, mean (SD)	84.0 (61.5)	75.9 (59.0)	.04
Yale vigorous activity index score, mean (SD)[e]	14.3 (15.3)	19.1 (17.7)	<.01
Genetic polymorphisms, no. (%)			
Apolipoprotein E ε4 allele	216 (29.2)	126 (32.3)	.27
Vitamin D receptor *Bsm*I BB genotype	96 (12.9)	49 (12.6)	.61
Vitamin D receptor *Fok*I ff genotype	75 (10.1)	44 (11.3)	.33
Miscellaneous risk factors			
Self-reported diabetes, no. (%)	154 (20.6)	62 (15.9)	.05
Body mass index, kg/m^2, mean (SD)	30.4 (7.5)	28.5 (5.4)	<.01
No past month alcohol consumption, no. (%)	352 (47.1)	114 (29.2)	<.01
Current smoker, no. (%)	136 (18.2)	106 (27.1)	.01

Note. All race/ethnicity groups were included (including African American admixture and others).
[a]*P* values reflect evaluation of differences by race/ethnicity from *t* statistics for continuous variables or from the χ^2 test for binary and categorical variables.
[b]Included only participants who had patella lead concentrations greater than zero.
[c]Daily intakes of dietary vitamin D and calcium were estimated on the basis of nutrition contents of vitamin D and calcium from consumption of a wide variety of food items over the past year including frequency, number of servings per ingestion, and the portion size.
[d]Time spent for each activity on the checklist was multiplied by an intensity (kcal/min) and was summed over all activities to create a total energy expenditure index for each participant.
[e]The frequency score was multiplied by the duration score to create a vigorous activity index score.

African Americans were 3.5 μg/g higher than among Whites ($P<.01$).

We next examined effect modification by potential moderators on the relations between tibia lead concentrations and selected covariates (using model 1). The relation between age and tibia lead concentrations was modified by gender (Table 4, model 2). The slope relating average tibia lead concentrations and age was 0.3 μg/g per year lower among women than among men ($P=.03$). The relation between self-reported diabetes status and tibia lead concentrations was also modified by race/ethnicity ($P<.01$; Table 4, model 3). On average, participants who reported diabetes had lower tibia lead concentrations than did those who did not; however, African Americans who reported diabetes had the highest average tibia lead concentrations: 6.5 μg/g higher than among African Americans without diabetes, and 8.7 μg/g higher than among Whites with diabetes.

Predictors of Patella Lead Concentrations

The proportion of women with negative patella lead values was almost twice that of men (29% vs 16%; data in this section not shown). In adjusted analyses, on average, participants who were older, male, wealthier, and who reported oral corticosteroid medication use had higher patella lead concentrations (data not shown). In evaluation of effect modification, the relation between gender and patella lead concentrations was modified by the *APOE* ε4 allele ($P=.04$). Mean patella lead concentrations among women without the *APOE* ε4 allele were approximately 11.8 μg/g lower than among men without the *APOE* ε4 allele; similarly, patella lead concentrations among men with the *APOE* ε4 allele were, on average, 5.0 μg/g lower than among men without the allele. However, patella lead concentrations among women with the allele were only 2.4 μg/g higher than among women without the allele.

Direct Comparison of Predictors of Patella and Tibia Lead Concentrations

In the simultaneous models, relations of gender, race/ethnicity, and the Yale energy index differed by bone site (each $P<.001$). Specifically, there was a larger patella–tibia bone lead concentration difference for men than for women, mainly because of the higher patella lead concentrations among men. In addition, there was a larger tibia–patella bone lead concentration difference for African Americans than for Whites, mainly because of higher tibia lead concentrations among African Americans. Finally, tibia lead concentrations increased with increasing Yale energy index, whereas patella lead concentrations very slightly declined.

DISCUSSION

In our large, population-based study of older adults in an urban setting with diversity by gender, race/ethnicity, and SES, we made observations that allowed us to draw several new inferences concerning the population burden of lifetime cumulative lead exposure; the factors that influence bone lead deposition and release; gender, race/ethnicity, and SES differences in lead dose; and the implications of these complex toxicokinetics for lead-related health outcomes with aging. Importantly, contrasting associations of predictor variables of patella lead concentrations with those of tibia lead concentrations allow hypotheses to be generated regarding cumulation and clearance of bone lead burden over time, which has important implications for health.

Differences by Race/Ethnicity

African Americans had higher tibia lead concentrations than did Whites, and this could

TABLE 3—Linear Regression Modeling Results Identifying Predictors of Blood Lead Concentrations: Baltimore Memory Study, Baltimore, Maryland, 2001–2005

	b (SE)	*P*
Model 1, adjusted r^2 = 13.6%		
Intercept	1.831 (0.170)	<.01
Tibia lead, ln(μg/dL)/μg/g	0.007 (0.002)	<.01
Female gender, ln(μg/dL)	−0.413 (0.053)	<.01
African American race/ethnicity, ln(μg/dL)	0.019 (0.054)	.73
Age, ln(μg/dL)/y	0.007 (0.004)	.11
Education, ln(μg/dL)	−0.002 (0.011)	.85
Body mass index,[a] ln(μg/dL)/kg/m^2	−0.015 (0.004)	<.01
Alcohol consumption past month, ln(μg/dL)	0.126 (0.053)	.02
Current smoker, ln(μg/dL)	0.167 (0.069)	.01
Dietary vitamin D, ln(μg/dL)/100 IU	−0.051 (0.017)	<.01
Supplemental calcium, ln(μg/dL)	−0.102 (0.050)	.04
Yale energy index, ln(μg/dL)/100 kcal/wk	0.001 (0.0004)	<.01
Yale vigorous activity index, ln(μg/dL)/unit	−0.005 (0.002)	<.01
Model 2,[b] adjusted r^2 = 14.0%		
Intercept	1.762 (0.173)	<.01
Female, ln(μg/dL)	−0.291 (0.074)	<.01
Yale vigorous activity index, ln(μg/dL)/unit	−0.0006 (0.002)	.79
Female × Yale vigorous activity index, ln(μg/dL)/unit	−0.007 (0.003)	.02
Model 3,[b] adjusted r^2 = 13.9%		
Intercept	1.912 (0.174)	<.01
Female, ln(μg/dL)	−0.490 (0.064)	<.01
African American, ln(μg/dL)	−0.126 (0.089)	.15
Female × African American, ln(μg/dL)	0.226 (0.108)	.04
Model 4,[b,c] adjusted r^2 = 12.2%		
Intercept	1.595 (0.214)	<.01
Taking hormone replacement therapy, ln(μg/dL)	−0.374 (0.065)	<.01

Note. ln = natural logarithm. Blood lead concentrations (μg/dL) were ln-transformed. Models were controlled for wealth (defined as the total dollar value of household assets plus total household income from visit 1 [in $10 000]) and self-reported history of kidney disease (yes vs no).

[a]Body mass index is weight in kilograms divided by height in meters squared.

[b]Models also included tibia lead concentration, gender, race/ethnicity, age, education, body mass index, tobacco consumption (nonsmoker, current smoker, and previous smoker), alcohol use in the past month (yes vs no), dietary vitamin D intake, supplemental calcium (yes vs no), Yale energy index, and Yale vigorous activity index.

[c]This model was confined to women only.

not be explained entirely by differences in SES (education and wealth) or other factors, suggesting that African Americans had higher cumulative lead doses from decades of higher environmental exposures. Notably, we may have underestimated the true tibia lead difference by race/ethnicity, because of the possible underrepresentation of African American men in the study.[33] The higher current tibia lead concentrations among African Americans were likely because of their larger lifetime cumulative exposures, rather than differential bone kinetics by race/ethnicity.

The kinetic issues are best evaluated in the more metabolically active patella,[7,8,50–52] and we believe that differential recent release of lead from bone by race/ethnicity is unlikely because (1) race/ethnicity was not associated with patella lead concentrations and (2) there was no effect modification by race/ethnicity on relations of patella lead concentrations with blood lead concentrations. Furthermore, in models of patella lead concentrations, the associations of age, oral corticosteroid use, gender, and the *APOE*–gender interaction, and in models of blood lead concentrations, the hormone replacement therapy and physical activity associations can all be interpreted as likely explained by bone-demineralization issues with aging.

Use of hormone replacement therapy was not associated with patella lead concentrations. The contrasting blood and patella associations could be caused by the relative amounts of lead in bone and blood, which differed by a factor of 200 to 1000 (for example, 400 times for 5 μg/dL in blood, 10 μg/g in bone, 5 L average blood volume, and 10 kg average dry skeletal mass). Thus, a relatively small release of lead from patella could change blood lead concentrations but would not change patella lead concentrations significantly. However, for logistical and budgetary reasons, lead concentrations in blood, tibias, and patellae were measured at different visits, so associations among them, particularly between blood lead concentrations and patella lead concentrations, could have been influenced by the timing of the measurements.

Differences by Age

Tibia lead concentrations were higher with increasing age. This could have been caused by either a cohort effect, because environmental lead concentrations were much higher in the past, or cumulation with age, or both. Because (1) the level of environmental lead exposure in the general population has been declining since the 1980s,[2] (2) the estimated clearance half-time of lead from tibias is approximately 30 years,[8] and (3) the turnover rate of bone mineral in tibias is much slower than in other bones,[51,52] we concluded that tibia lead concentrations likely were most reflective of lifetime cumulative dose, most of which occurred decades ago.

Increasing age was also associated with higher patella lead concentrations. In addition, patella lead concentrations were lower, on average, than tibia concentrations; there were many more negative values; the proportion of negative patella lead values was almost twice as large for women as for men; and the relation of gender with bone lead concentrations differed by bone lead site (in the simultaneous modeling).

Taken together, we believe these findings offer clues about the relative clearance of lead and bone mineral from trabecular bone

TABLE 4—Tobit Regression Modeling Results Identifying Predictors of Tibia Lead Concentrations: Baltimore Memory Study, Baltimore, Maryland, 2001–2005

	b (SE)[a]	*P*
Model 1, adjusted r^2 = 10.4%		
Intercept	19.00 (2.94)	<.01
Age, μg/g/y	0.37 (0.07)	<.01
African American, μg/g	3.53 (0.88)	<.01
Yale energy index, μg/g/100 kcal/wk	0.02 (0.01)	<.01
Dietary calcium, μg/g/100 mg	−0.32 (0.10)	<.01
Dietary vitamin D, μg/g/100 IU	1.26 (0.47)	<.01
Model 2,[b] adjusted r^2 = 10.8%		
Intercept	19.34 (2.71)	<.01
Age, μg/g/y	0.57 (0.10)	<.01
Female, μg/g	0.20 (0.77)	.80
Female × age, μg/g/y	−0.30 (0.14)	.03
Model 3,[b] adjusted r^2 = 11.3%		
Intercept	19.79 (2.92)	<.01
African American, μg/g	2.24 (0.90)	.01
Diabetes, μg/g	−2.73 (1.63)	.09
African American × diabetes, μg/g	6.46 (2.33)	<.01

Notes. Tobit was used to model data whose distribution was truncated or censored, in this case primarily because of the negative values in the tibia lead distribution. Models controlled for gender, education, wealth (defined as the total dollar value of household assets plus total household income from visit 1 [in $10 000]), body mass index (weight in kilograms divided by height in meters squared), tobacco consumption (nonsmoker, current smoker, and previous smoker), alcohol use in the past month (yes vs no), current oral corticosteroid medication use (yes vs no), and supplemental vitamin C use (yes vs no).
[a]Robust estimates.
[b]Models also included age, race/ethnicity, Yale energy index, and dietary calcium and vitamin D intakes.

with increasing age. Bone mineral density, particularly in trabecular bone such as patellae, is known to decline with age after the peak bone mass is achieved at age 18 to 25 years.[51,53] Our findings suggest that bone mineral may be more rapidly lost from patellae than lead itself, because bone mineral is the denominator in the bone lead concentration. This could occur, for example, if lead were not distributed homogeneously in bone, particularly if it were at higher concentrations in periosteal bone.

We did not observe associations between the 3 lead biomarkers and *VDR* and *APOE* genotypes, in contrast to findings from occupational studies.[38,54] This may be because of lower concentrations of lead in all tissues in nonoccupational studies. However, in adjusted analysis of patella lead concentrations, there was evidence of effect modification by *APOE* genotype on relations of gender with patella lead concentrations. The *APOE* ε4 allele is associated with lower bone mineral density and higher bone turnover rates[40,55]; our findings may suggest that among men, the allele was associated with lead loss that exceeded bone mineral loss, but among women, the allele was associated with bone mineral loss that exceeded lead loss, as might be expected.

The racial/ethnic difference in tibia lead concentrations was consistent with historical blood lead concentration data in national samples, which have shown important differences by race/ethnicity.[56,57] Our study is the first population-based study to compare bone lead concentrations by race/ethnicity. The high average tibia lead concentration among both Whites and African Americans is an ongoing risk for the development of chronic lead-related health effects with aging, and this risk may be higher among African Americans because of their higher lifetime cumulative doses. These health effects include cognitive,[58,59] cardiovascular,[60,61] and renal[62,63] outcomes.

Furthermore, the race/ethnicity–diabetes interaction suggests that tibia lead concentrations were highest in African Americans with diabetes, a combination of 3 risk factors that could contribute to disparities in these important racial/ethnic–associated health outcomes. An implication of our findings is that the racial/ethnic differences in chronic disease outcomes reported in prior studies may have resulted from unmeasured confounding by differences in cumulative lead dose. However, it can be difficult to "separate" the effect of race/ethnicity from cumulative lead dose in health studies.[64,65]

Implications for Health

The findings have implications for population aging. For example, a proportion of what has been termed "normal cognitive aging" may be caused, at least in part, by cumulative lead dose.[58] However, there is no population surveillance of cumulative lead burden among US adults. Use of lead in gasoline peaked in 1969, but the magnitude of the public health implications of the coming collision of population aging—both in terms of numbers and ages attained—with peak lead dosing in early life and midlife, is not understood. Determining how lead will contribute to the coming epidemic of neurodegenerative disease, cognitive decline, and dementia[66–68] should be a major public health priority. Furthermore, screening and clinical and public health interventions may be especially warranted in the high-risk groups identified in this study (e.g., African Americans, women).

We conclude that there are large and important differences in lead biomarkers by gender, race/ethnicity, and several additional factors (e.g., physical activity, dietary intake) that could influence the kinetics of these measures. African Americans have significantly higher current body burdens of lead, likely because of sustained higher ongoing lead exposures over decades. With disease occurrence and bone demineralization with age, women and African Americans would be at higher risk of a number of adverse lead-related health outcomes as they age. The extent to which the differential lifetime cumulative lead dose contributes to observed differences in health status by race/ethnicity needs to be investigated, as do possible interventions to prevent lead-related health outcomes with aging. ■

About the Authors

Keson Theppeang and Brian S. Schwartz are with the Department of Environmental Health Sciences, Division of Occupational and Environmental Health; Thomas A. Glass and Brian S. Schwartz are with the Department of Epidemiology; and Keson Theppeang, Karen Bandeen-Roche, and Charles A. Rohde are with the Department of Biostatistics, all at the Johns Hopkins Bloomberg School of Public Health, Baltimore, MD. Andrew C. Todd is with the Department of Community and Preventive Medicine, Mount Sinai School of Medicine, New York, NY.

Requests for reprints should be sent to Brian S. Schwartz, Johns Hopkins University, Bloomberg School of Public Health, 615 North Wolfe St, Room W7041, Baltimore, MD 21205 (e-mail: bschwart@jhsph.edu).

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Contributors

B.S. Schwartz and K. Theppeang originated the bone mineral density substudy. B.S. Schwartz, T.A. Glass, and K. Bandeen-Roche originated and designed the parent study. B.S. Schwartz supervised all aspects of the substudy, and K. Theppeang performed or assisted with recruitment, enrollment, data collection, analysis, and preparation of the first draft of the article describing the substudy. K. Bandeen-Roche and C. Rohde supervised the data analysis. A.C. Todd assisted with data collection and supervised the measurement of bone lead concentrations. All authors helped to conceptualize ideas, interpret findings, and edit drafts of the article.

Human Participant Protection

The study was approved by Committee for Human Research at the Johns Hopkins Bloomberg School of Public Health.

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