

Associations of Patella Lead and Other Lead Biomarkers With Renal Function in Lead Workers

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Objective: We sought to compare associations of patella lead, which may represent a unique cumulative and bioavailable lead pool, with other lead measures in models of renal function. **Methods:** Renal function measures included blood urea nitrogen, serum creatinine, measured and calculated creatinine clearances, and urinary *N*-acetyl- β -*D*-glucosaminidase (NAG) and retinol-binding protein. **Results:** In 652 lead workers, mean (SD) blood, patella, and tibia lead were 30.9 (16.7) μ g/dL, 75.1 (101.1) and 33.6 (43.4) μ g Pb/g bone mineral, respectively, and were correlated (Spearman's $r = 0.51-0.74$). Patella lead was associated ($P < 0.05$) with NAG in all lead workers. In models of effect modification by age, higher patella lead also was associated with higher serum creatinine in older participants. Similar associations were observed for blood and tibia lead. **Conclusions:** Associations between patella lead and adverse renal outcomes were not unique; this may be due, in part, to high correlations among the lead biomarkers in this study. (J Occup Environ Med. 2005;47:235-243)

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Inorganic lead is a cumulative toxicant that is stored in bone. Several lead dose measures are available, and each is thought to estimate a different biological lead pool. Blood lead is a relatively short-term measure (ie, half-life of 30 days¹) that reflects exposure from current exogenous sources and the release of lead from internal lead stores. Bone is both a repository and a source of lead; the latter occurs in steady state as well as pathologic bone conditions, such as osteoporosis.¹ Lead in trabecular bone (commonly measured in the patella or calcaneus) is more bioavailable than lead in cortical bone (measured in the midtibia) and has a shorter half-life.^{1,2} An additional lead measure, chelatable lead, is thought to represent a bioavailable pool of lead from blood, soft tissue, and bone. Blood lead is considered the best measure of recent dose (although, as noted, it does not reflect this solely) and tibia lead is the best measure of cumulative dose. However, bioavailability also must be considered, and patella lead may be the best measure of lead dose that is both cumulative and bioavailable. A determination of which lead biomarkers are associated with decreased renal function would be useful for future research as well as for improvement of medical surveillance in exposed populations.

We recently reported associations between lead measures and renal function in data from the initial evaluation in a longitudinal study of 803 current and former lead workers in

South Korea.³ We studied a range of renal outcomes, including clinical (blood urea nitrogen [BUN], serum creatinine, measured and calculated creatinine clearances) and early biological effect (*N*-acetyl- β -D-glucosaminidase [NAG] and retinol-binding protein [RBP]) measures. Lead biomarkers included tibia, blood, and dimercaptosuccinic acid (DMSA)-chelatable lead. Analysis of these data suggested that both recent and cumulative lead, in the dose range studied, adversely impact renal function; this effect was most evident in older workers.

Patella lead was obtained at the third annual evaluation in this study. Therefore, to compare and contrast associations of patella lead with other lead measures, we performed a cross-sectional analysis of data from the 652 lead workers who participated in that evaluation. Exposure assessment included patella, blood, and 4-hour DMSA-chelatable lead from the third evaluation, as well as tibia lead, which was obtained at the second evaluation. The same set of renal outcome measures was obtained at the third evaluation.

Materials and Methods

Study Overview and Design

We performed a cross-sectional analysis of data from the 652 current and former lead workers who completed the third annual evaluation in a longitudinal study of the adverse health effects of inorganic lead exposure. Evaluations were performed between December 19, 1999, and June 24, 2001. All participants provided written, informed consent. The study protocol was approved by Institutional Review Boards at the SoonChunHyang University School of Medicine and the Johns Hopkins University Bloomberg School of Public Health. Participation in the study was voluntary, and workers were paid approximately \$30 for their time and effort.

Study Population

As previously described,^{3,4} workers were recruited from 26 plants that 1) produced lead batteries, lead oxide, lead crystal, or radiators or 2) were secondary lead smelters. Workers were designated as lead workers based on the potential for exposure to lead in the manufacturing process. No medical exclusionary criteria were used. Study participants were not currently occupationally exposed to other known renal toxicants.

Data Collection

Data collection was completed either at the Institute of Industrial Medicine of the SoonChunHyang University in Chonan or at the study plants using previously reported methods.^{3,4} Pertinent data and biologic specimens collected included a standardized questionnaire on demographics, medical history, and occupational history; blood pressure, height and weight measurements; a blood specimen (for blood lead, BUN, and serum creatinine), a spot urine sample (for NAG, RBP, and creatinine), and a patella lead measurement. Tibia lead, obtained in the second evaluation, was available for the subset of workers ($n = 574$) who participated in both the second and third evaluations. Among these subjects, there was an average of 398 days between the two evaluations. A 4-hour urine collection after oral administration of 10 mg/kg DMSA was also obtained to measure DMSA-chelatable lead and creatinine clearance.

Laboratory Methods

The lead biomarkers and renal outcomes were measured using previously reported methods.^{3,4} In brief, blood lead was measured with an Hitachi 8100 Zeeman background-corrected atomic absorption spectrophotometer (Hitachi Ltd. Instruments, Tokyo, Japan)⁵ at the Institute of Industrial Medicine, a certified reference laboratory for lead in South Korea. Patella and tibia lead

levels were assessed via a 30-minute measurement of the left medial patella and midtibia diaphysis, respectively, using ¹⁰⁹Cd in a back-scatter geometry to fluoresce the K-shell x-rays of lead. The lead x-rays were recorded with a radiation detector and then quantified and compared with calibration data to estimate the concentration of lead in bone.^{6,7} Emitted K-shell x-rays are attenuated as they pass through bone and overlying tissues. The lead x-rays were therefore normalized to the amount of elastic scattering from the bone itself to yield a measurement accuracy that is independent of the distance between the radiation source and the subject; subject positioning; small subject movements; overlying tissue thickness; and bone size, shape, geometry, and density.⁶⁻⁹ All point estimates, including negative values, were retained in the statistical analyses to minimize bias and to avoid censoring of data.¹⁰ Urine lead levels in the 4-hour collection were measured at the Wadsworth Center of the New York State Department of Health (Albany, NY) by electrothermal atomic absorption spectrometry with Zeeman background correction (Model 4100ZL, Perkin-Elmer, Norwalk, CT).¹¹

BUN and serum creatinine were measured via an automatic chemical analyzer (model TBA 40FR Biochemical Analyzer; Toshiba, Tokyo, Japan). Urine creatinine was measured with the Sigma kit (St. Louis, MO). Measured creatinine clearance was defined as: ([urinary creatinine in mg/dL \times urine volume in ml] / serum creatinine in mg/dL) / collection time in minutes. Calculated creatinine clearance was obtained from the Cockcroft-Gault equation.¹² NAG activity (expressed in μ mol substrate converted per hour) was measured using the P.P.R. NAG test kit (P.P.R. Diagnostics, Ltd.; London, UK), and RBP was measured using a modification of the method of Topping and coworkers.¹³ Mean between-day coefficients of variation for 84 random NAG samples and

169 random RBP samples assayed in duplicate were both 8.7% (RBP duplicates were performed within 6 weeks of the initial assay).

Statistical Analysis

The goals of the analysis were to 1) compare and contrast associations between patella lead and six renal outcomes (BUN, serum creatinine, measured creatinine clearance, calculated creatinine clearance, RBP, and NAG) with associations of the three other lead dose biomarkers (tibia lead from the second evaluation, blood lead, DMSA-chelatable lead) in current and former lead workers while controlling for covariates; and 2) to evaluate whether age modified those associations, also controlling for covariates. Statistical analysis was completed using software programs of the SAS Institute, Inc. (Cary, NC).

Initially, variable distributions were examined. The distributions of NAG and RBP showed departures from normality and were thus \ln -transformed; the adequacy of this transformation was subsequently confirmed by examination of the residuals from the final regression models. The SAS t test procedure (including the Satterthwaite test for unequal variances) was used to compare means for the selected demographic, exposure, and health outcome measures from the initial evaluation of the 652 lead workers who completed the third evaluation with those from the 153 who did not. χ^2 testing was used when these measures were dichotomous. Linear regression modeling was used to evaluate associations between lead measures and renal outcomes. Covariate selection used a priori variables (age, gender, and body mass index [BMI; weight in kilograms divided by the square of height in meters]) in modeling that initially included other biologically relevant variables in separate models. Variables with P values <0.1 were then modeled together and those with P values <0.1 in the combined model

were retained. Additional covariates assessed included diabetes and hypertension (both based on participant report of physician diagnosis), use of analgesics (based on questionnaire data on medication usage), work status (current versus former lead worker), systolic and diastolic blood pressure, tobacco use, and alcohol consumption. Final BUN, serum creatinine, measured creatinine clearance, and calculated creatinine clearance models were adjusted for age, gender, BMI, work status, hypertension, diabetes, use of analgesics, and smoking status (current, ex, never). NAG and RBP models were adjusted for age, gender, BMI, work status, systolic blood pressure, diabetes, and smoking status. Continuous independent variables were centered at the mean, except for the effect modification by age models, discussed below, in which age was centered at the 67th percentile.

Next, models with cross-product terms of the lead measures and age were evaluated to determine whether age modified relations between the lead measures and renal outcomes. Initially, the age range was divided into tertiles; examination of these models revealed consistencies among associations between the lead measures and the renal outcomes in participants whose ages were in the youngest and middle tertiles. Therefore, these tertiles were combined and age was dichotomized at the 67th percentile (48.8 years) in the final models. To avoid residual age confounding, continuous age (centered at the 67th percentile) was entered as an independent variable instead of the categorical age variables that were used in the cross-product terms.

As in previous analyses,³ models were evaluated for linear regression assumptions and the presence of outlying points using added variable plots,¹⁴ which are graphical summaries of the relation between Y and a particular X , adjusted for all of the other covariates. Each plot displays residuals and two lines: the regres-

sion line, and a line determined by a scatter plot smoothing method (lowess) that calculates a locally weighted least-squares estimate for each point in the scatter plot.¹⁵ These lines allow an examination of the data for outliers that are overly influential, as evidenced by inconsistency between the lowess and regression lines. The “lowess” function of the S-plus statistical software program (MathSoft, Seattle, WA) was used to produce these plots. When applicable, models were repeated without outliers. Models also were assessed for collinearity through the examination of variance inflation factors and conditional indices.

Results

Selected Demographics, Exposure, and Health Outcome Measures

Information on demographics, lead biomarkers, renal function, and selected covariates from the third evaluation is presented in Table 1 for all lead workers and separately by the two groups used in models of effect modification by age. Women and former lead workers were well represented in the third evaluation population, particularly in the oldest third of the population. Mean (SD) patella, blood, tibia (at the second evaluation), and DMSA-chelatable lead levels in all lead workers were 75.1 (101.1) $\mu\text{g Pb/g}$ bone mineral, 30.9 (16.7) $\mu\text{g/dL}$, 33.6 (43.4) $\mu\text{g Pb/g}$ bone mineral, and 0.63 (0.75) $\mu\text{g/mg}$ creatinine, respectively. All except blood lead were substantially higher in the older age group. Ranges for the lead biomarkers were wide. The biomarkers were highly correlated (Table 2). Mean values for the clinical renal outcomes (BUN, serum creatinine, measured and estimated creatinine clearances) were normal, although the range for each included several abnormal values. On the basis of data from the first evaluation, the 652 lead workers who completed the third evaluation were, on average, older, more likely to be women,

TABLE 1

Selected Demographic, Exposure, and Health Outcome Measures From the Third Evaluation in Current and Former Lead Workers

Characteristic	All Participants, n = 652		Youngest 67%, Age <48.8 Years, n = 440		Oldest 33%, Age ≥48.8 Years, n = 212		
	Number	%	Number	%	Number	%	
Sex							
Male	503	77.2	387	88.0	116	54.7	
Female	149	22.8	53	12.0	96	45.3	
Work status							
Current lead worker	452	69.3	334	75.9	118	55.7	
Former lead worker	200	30.7	106	24.1	94	44.3	
Diabetes	8	1.2	4	0.9	4	1.9	
Hypertension	53	8.1	25	5.7	28	13.2	
Regular analgesic use	27	4.1	9	2.1	17	8.0	
Smoking							
Never smokers	222	34.2	112	25.5	110	52.1	
Current smokers	326	50.2	260	59.2	66	31.3	
Ex-smokers	102	15.7	67	15.3	35	16.6	
	Mean	SD	Range	Mean	SD	Mean	SD
Age, years	43.3	9.8	20.0–67.7	38.1	6.9	54.3	3.8
BMI, kg/m ²	23.5	3.0	16.0–37.5	23.3	2.9	24.0	3.1
Systolic blood pressure, mm Hg	120.7	16.3	83.3–211.3	118.1	13.6	126.1	19.8
Diastolic blood pressure, mm Hg	74.1	12.6	26.0–131.3	72.4	11.9	77.5	13.2
Patella lead, μg Pb/g bone mineral	75.1	101.1	–11.8–946.1	54.3	61.8	118.3	144.2
Blood lead, μg/dL	30.9	16.7	4.0–89.2	30.2	15.6	32.4	18.7
Tibia lead, μg Pb/g bone mineral*	33.6	43.4	–17.8–334.0	25.4	31.0	50.1	58.1
DMSA-chelatable lead, μg Pb/mg creatinine	0.63	0.75	0.01–5.69	0.53	0.60	0.83	0.97
Lead job duration, year	10.0	6.5	<1–36.3	8.81	5.5	12.5	7.8
BUN, mg/dL	14.4	3.9	5.1–38.9	14.1	3.5	14.9	4.6
Serum creatinine, mg/dL	0.87	0.15	0.51–2.26	0.88	0.13	0.86	0.20
Measured creatinine clearance, mL/min	109.2	34.8	17.8–447.0	116.1	36.5	94.9	25.8
Calculated creatinine clearance, mL/min	97.0	22.5	25.7–182.4	104.5	20.9	81.6	17.3
NAG, μmol/h/g creatinine	207.5	173.7	13.9–1833.5	177.4	121.6	269.9	237.5
RBP, μg/g creatinine	65.8	353.5	2.5–8363.5	41.9	51.5	115.2	613.1

*Because tibia lead was measured in the second evaluation, there were 574 workers who completed both the second and third evaluations.

TABLE 2

Spearman Correlation Coefficients for Age and the Lead Biomarkers in 652 Current and Former Lead Workers*

	Patella Lead	Blood Lead	Chelatable Lead	Tibia Lead†
Age	0.41	0.06	0.17	0.33
Patella lead		0.66	0.59	0.74
Blood lead			0.76	0.57
Chelatable lead				0.51

*P values for all correlations were <0.0001 except for blood lead and age, for which P = 0.15.

†Tibia lead was measured in the second evaluation; thus, there were 574 workers who completed both the second and third evaluations.

and had longer durations in lead exposed jobs compared with the 153 leaders who did not (Table 3). No consistent differences were found in mean levels of the lead biomarkers or renal outcomes in the two groups.

Associations of Lead Measures with Renal Outcomes

Associations between lead measures and renal outcomes, after removal of influential outliers, are

shown in Table 4 (β coefficients and standard errors of the β coefficients for patella, blood, and tibia lead have been multiplied by 10^2). Patella lead was significantly ($P < 0.05$) associated with NAG, as were blood and DMSA-chelatable lead. Patella lead was not associated with any of the four clinical renal outcomes; however, higher DMSA-chelatable lead was associated with lower serum creatinine and higher calculated creatinine clearance.

Effect Modification by Age on Associations of Lead Measures with Renal Outcomes

Regression models were next performed to evaluate whether age, di-

TABLE 3

Selected Demographic, Exposure, and Health Outcome Measures From the First Evaluation of the 652 Lead Workers Who Completed the Third Evaluation Compared With Measures From the 153 Who Did Not*

Initial Evaluation Characteristic	Third Evaluation, Completers (n = 652)		Third Evaluation, Noncompleters (n = 153)		P Value
	Number	%	Number	%	
Sex					
Male	503	77.2	137	89.5	
Female	149	22.8	16	10.5	<0.01
Work status					
Current lead worker	569	87.3	141	92.2	
Former lead worker	83	12.7	12	7.8	0.09
Hypertension	48	7.4	10	6.5	0.72
	Mean	SD	Mean	SD	
Age, years	41.1	9.7	37.8	11.4	<0.01
Lead job duration, years	8.4	6.4	6.6	6.7	<0.01
Blood lead, $\mu\text{g}/\text{dL}$	31.9	14.8	32.4	16.0	0.71
Tibia lead, $\mu\text{g}/\text{g}$	37.5	41.8	35.8	33.5	0.59
DMSA-chelatable lead, $\mu\text{g Pb}/\text{mg creatinine}$	0.77	0.86	0.76	0.87	0.90
BUN	14.5	3.6	13.8	3.8	0.03
Serum creatinine	0.90	0.16	0.92	0.18	0.10

*Published analyses of the first evaluation included 803 lead workers; 2 others were enrolled later.

chotomized at the 67th percentile (48.8 years), modified relations among the lead biomarkers and renal outcomes. Evidence of effect modification by age on relations between lead measures and renal outcomes was observed (Table 5; β coefficients and standard errors of the β coefficients for patella, blood, and tibia lead have been multiplied by 10^2). In participants in the oldest age group, higher patella lead was associated with higher serum creatinine and NAG. Similar associations were observed for blood and tibia lead. However, in the group of workers whose ages were in the youngest two thirds of the age range, the beta coefficients for these associations were smaller, although the difference between slopes in the two age groups was statistically significant only for the association of blood lead and serum creatinine. The effect modification by age on the association between patella lead and serum creatinine is shown graphically in Fig. 1. In contrast, DMSA-chelatable lead

was associated with lower serum creatinine and higher calculated creatinine clearance in the workers in the younger age group. However, in models of NAG, similar to the other lead measures, DMSA-chelatable lead was significantly associated in participants in the older age group.

Discussion

In this cross-sectional analysis of data from the third evaluation in a longitudinal study of Korean lead workers, we compared associations of patella lead with renal function to associations of three other lead measures with the same outcomes. In all lead workers, patella lead was associated with NAG, as were blood and DMSA-chelatable lead. In contrast, higher DMSA-chelatable lead also was associated with lower serum creatinine and higher calculated creatinine clearance. In models that assessed effect modification by age, higher patella lead also was associated with higher serum creatinine among participants in the oldest age

tertile. Similar associations were observed for blood and tibia lead. Beta coefficients were less in the lead workers whose ages were in the younger two thirds of the age range, although the difference between slopes in the two age groups was statistically significant only for the association of blood lead and serum creatinine. In contrast, higher DMSA-chelatable lead was associated with lower serum creatinine and higher calculated creatinine clearance in younger workers but with higher NAG in older participants.

In this report, we compared patella lead associations with associations of three other lead biomarkers by using data from the third evaluation (with the exception of tibia lead). However, associations for the three lead biomarkers obtained in the first evaluation are likely to be the most valid because the number of study participants was greater. A comparison of associations of patella lead with renal outcomes from the third evaluation to associations of blood, tibia, and DMSA-chelatable lead with renal outcomes from the first evaluation (conducted a mean of 2.2 years earlier in the original cohort of 803 lead workers³) reveals consistent findings. Higher blood and tibia lead levels were associated with decreased renal function in those workers whose ages were in the oldest tertile; beta coefficients were in the opposite direction in the youngest age group for the clinical outcomes but not for NAG. The inverse association between DMSA-chelatable lead and serum creatinine was significant in the first evaluation and present but not significant ($P = 0.14$) in the model of calculated creatinine clearance. Beta coefficients in Table 5 are also consistent with those from the first evaluation. Overall, in our data, patella lead associations were similar to the other three lead biomarkers in models of NAG and consistent with all but DMSA-chelatable lead in models of the clinical renal outcomes.

TABLE 4

Linear Regression Modeling of Associations Between Lead Biomarkers and Renal Outcomes in Current and Former Lead Workers*

Renal Outcomes	β Coeff†	SE β †	P Value	Model r^2
Associations of patella lead, $\mu\text{g Pb/g}$ bone				
BUN (mg/dL)	0.1097	0.1857	0.56	0.09
Serum creatinine (mg/dL)	0.0078	0.0062	0.21	0.27
Measured creatinine clearance (ml/min)	0.6369	1.5299	0.68	0.24
Calculated creatinine clearance (ml/min)	-0.6834	0.7802	0.38	0.58
ln NAG (ln [$\mu\text{mol/h/g}$ creatinine])	0.0906	0.0349	0.01	0.15
ln RBP (ln [$\mu\text{g/g}$ creatinine])	-0.0349	0.0391	0.37	0.10
Associations of blood lead, $\mu\text{g/dL}$				
BUN (mg/dL)	0.4190	1.1271	0.71	0.08
Serum creatinine (mg/dL)	0.0416	0.0374	0.27	0.28
Measured creatinine clearance (ml/min)	0.0757	9.0450	0.99	0.24
Calculated creatinine clearance (ml/min)	-3.0878	4.7260	0.51	0.58
ln NAG (ln [$\mu\text{mol/h/g}$ creatinine])	0.5154	0.1999	0.01	0.14
ln RBP (ln [$\mu\text{g/g}$ creatinine])	-0.0189	0.2256	0.93	0.10
Associations of tibia lead, $\mu\text{g Pb/g}$ bone‡				
BUN (mg/dL)	0.3282	0.4399	0.46	0.09
Serum creatinine (mg/dL)	0.0281	0.0147	0.06	0.29
Measured creatinine clearance (ml/min)	3.3235	3.5788	0.35	0.23
Calculated creatinine clearance (ml/min)	-2.3366	1.7906	0.19	0.58
ln NAG (ln [$\mu\text{mol/h/g}$ creatinine])	0.0999	0.0778	0.20	0.13
ln RBP (ln [$\mu\text{g/g}$ creatinine])	-0.0813	0.0868	0.35	0.09
Associations of DMSA-chelatable lead, $\mu\text{g Pb/mg}$ creatinine				
BUN (mg/dL)	0.0510	0.2451	0.84	0.08
Serum creatinine (mg/dL)	-0.0238	0.0080	<0.01	0.29
Measured creatinine clearance (ml/min)	-0.3107	1.9684	0.88	0.24
Calculated creatinine clearance (ml/min)	3.2849	1.0068	<0.01	0.59
ln NAG (ln [$\mu\text{mol/h/g}$ creatinine])	0.1074	0.0393	<0.01	0.14
ln RBP (ln [$\mu\text{g/g}$ creatinine])	-0.0061	0.0444	0.89	0.10

*The renal outcomes were each modeled separately, with one of the four lead measures included at a time (resulting in a total of 24 models). Regression results from each model are presented only for the association of the lead measure with the renal outcome. BUN, serum creatinine, 4-hour creatinine clearance, and calculated creatinine clearance models were adjusted for age, gender, BMI, work status (current vs. former lead worker), hypertension, diabetes, use of analgesics and smoking status (current, ex, never). NAG and RBP models were adjusted for age, gender, BMI, work status, systolic blood pressure, diabetes, and smoking status.

† β coefficients and standard errors of the β coefficients for patella, blood, and tibia lead have been multiplied by 10^2

‡ $n = 574$ in models with tibia, since this lead biomarker was obtained in the second evaluation of the study.

Few studies have examined associations between bone lead and renal outcomes; fewer still have reported associations with patella lead. Wu and coworkers¹⁶ studied associations

among three lead measures and two renal outcomes in participants in the Normative Aging Study. These authors reported significant ($P < 0.05$) and borderline significant ($P = 0.08$)

associations of higher patella and tibia lead, respectively, with lower creatinine clearance (estimated by the Cockcroft-Gault equation). No significant associations with serum creatinine were observed, and blood lead was not associated with either renal outcome. In contrast, an association between higher tibia lead and higher 2-hour measured creatinine clearance was found in a combined group of 76 lead workers and 68 controls (mean blood lead = 14.1 $\mu\text{g/dL}$ in the control group).¹⁷ No significant associations between tibia lead and the other renal outcomes studied, including serum creatinine, NAG, and RBP, were observed. Blood lead was not associated with any of the renal outcomes. Gehardsson and colleagues¹⁸ found no significant correlations between NAG and either calcaneus or tibia lead in 70 current or 30 retired lead workers.

These seemingly inconsistent results may be the result of lead-induced hyperfiltration, in which initial inverse associations (such as higher lead measures with higher creatinine clearance) subsequently evolve, with continued exposure and/or progression of renal damage, into associations of higher lead measures with worse renal function (eg, lower creatinine clearance). This pattern of progression has been observed in rats with high lead exposure,¹⁹ although less so with lower lead exposure.²⁰ The mean ages of the lead workers in the studies cited above were 43.6¹⁷ and 37.4 years,¹⁸ respectively. The mean age of workers in our oldest tertile was 54.1 years and the mean age of the Normative Aging population was 67.0 years.¹⁶ Thus, the inverse association between higher tibia lead and creatinine clearance noted by Roels and colleagues¹⁷ was in a relatively younger population compared with the participants in our oldest tertile and in the Normative Aging Study in whom associations between higher lead measures and worse renal function were observed. Analyses of data from the first evaluation of this Ko-

TABLE 5

Linear Regression Modeling of Effect Modification by Age, Dichotomized at the 67th Percentile, on Associations Between Lead Biomarkers and Renal Outcomes in Current and Former Lead Workers*

Lead Measure	Serum Creatinine (mg/dL)			Calc. Creatinine Clearance (mL/min)			In NAG (ln [$\mu\text{mol/h/g creatinine}$])		
	β coeff.	SE β	P Value	β Coeff.	SE β	P Value	β coeff.	SE β	P Value
Intercept	0.9077	0.0139	<0.01	90.8048	1.7817	<0.01	4.9017	0.0727	<0.01
Age, years	0.0000	0.0006	0.99	-1.2045	0.0760	<0.01	0.0155	0.0033	<0.01
Patella lead, $\mu\text{g Pb/g bone}^{**}$	0.0147	0.0073	0.04	-1.0268	0.9237	0.27	0.1013	0.0409	0.01
Patella lead, $\mu\text{g/g} \times \text{agecat 1}$	-0.0196	0.0134	0.15	1.4296	1.7136	0.40	-0.0383	0.0739	0.60
Intercept	0.9098	0.0138	<0.01	90.6456	1.7572	<0.01	4.9237	0.0718	<0.01
Age, years	-0.0000	0.0006	0.95	-1.1997	0.0704	<0.01	0.0161	0.0031	<0.01
Blood lead, $\mu\text{g/dL}^{**}$	0.1266	0.0528	0.02	-9.2336	6.6729	0.17	0.7155	0.2705	<0.01
Blood lead, $\mu\text{g/dL} \times \text{agecat 1}$	-0.1166	0.0573	0.04	9.6132	7.2527	0.19	-0.2863	0.3041	0.35
Intercept	0.9192	0.0149	<0.01	89.5705	1.8590	<0.01	4.9133	0.0783	<0.01
Age, years	0.0000	0.0006	0.95	-1.2087	0.0789	<0.01	0.0164	0.0035	<0.01
Tibia lead, $\mu\text{g Pb/g bone}^{**}$	0.0451	0.0215	0.04	-3.5907	2.6725	0.18	0.3017	0.1197	0.01
Tibia lead, $\mu\text{g/g} \times \text{agecat 1}$	-0.0288	0.0319	0.37	2.9452	3.9718	0.46	-0.2098	0.1775	0.24
Intercept	0.9181	0.0135	<0.01	89.6625	1.7004	<0.01	4.9282	0.0710	<0.01
Age, years	0.0007	0.0005	0.18	-1.2966	0.0690	<0.01	0.0156	0.0031	<0.01
Chelatable lead, $\mu\text{g Pb/mg creat}^{**}$	0.0013	0.0114	0.91	-0.2481	1.4307	0.86	0.1852	0.0614	<0.01
Chelatable lead, $\mu\text{g/mg} \times \text{agecat 1}$	-0.0384	0.0147	<0.01	5.7096	1.8455	<0.01	-0.0686	0.0772	0.37
Lead measure	β Coeff.	SE β	P Value	Measured creatinine clearance (mL/min)	SE β	P Value	In RBP (ln [$\mu\text{g/g creatinine}$])	SE β	P Value
Intercept	16.0244	0.4163	<0.01	107.6290	3.3572	<0.01	3.3498	0.0769	<0.01
Age, years	0.0691	0.0178	<0.01	-0.6898	0.1443	<0.01	0.0123	0.0035	<0.01
Patella lead, $\mu\text{g Pb/g bone}^{**}$	0.2086	0.2187	0.34	0.6300	1.8355	0.73	0.0134	0.0434	0.76
Patella lead, $\mu\text{g/g} \times \text{agecat 1}$	-0.3368	0.4012	0.40	-0.2256	3.2666	0.95	-0.0822	0.0782	0.29
Intercept	15.9585	0.4140	<0.01	108.0087	3.3090	<0.01	3.3897	0.0768	<0.01
Age, years	0.0699	0.0166	<0.01	-0.6712	0.1334	<0.01	0.0110	0.0033	<0.01
Blood lead, $\mu\text{g/dL}^{**}$	1.6102	1.5788	0.31	2.6537	12.8162	0.84	0.0439	0.2928	0.88
Blood lead, $\mu\text{g/dL} \times \text{agecat 1}$	-2.0078	1.7093	0.24	1.2515	13.7722	0.93	0.0228	0.3283	0.94
Intercept	15.9899	0.4432	<0.01	108.1007	3.6184	<0.01	3.3502	0.0812	<0.01
Age, years	0.0841	0.0189	<0.01	-0.6327	0.1544	<0.01	0.0082	0.0037	0.03
Tibia lead, $\mu\text{g Pb/g bone}^{**}$	0.4525	0.6169	0.46	-0.8268	5.0475	0.87	0.1116	0.1202	0.35
Tibia lead, $\mu\text{g/g} \times \text{agecat 1}$	-1.0705	0.9421	0.26	3.6302	7.6382	0.63	-0.1659	0.1817	0.36
Intercept	15.9888	0.4112	<0.01	108.3458	3.2800	<0.01	3.3888	0.0764	<0.01
Age, years	0.0750	0.0167	<0.01	-0.6133	0.1333	<0.01	0.0109	0.0033	<0.01
Chelatable lead, $\mu\text{g Pb/mg creat}^{**}$	0.2868	0.3570	0.42	1.0191	2.8987	0.73	0.0415	0.0670	0.54
Chelatable lead, $\mu\text{g/mg} \times \text{agecat 1}$	-0.5370	0.4525	0.24	-2.5606	3.6490	0.48	-0.0676	0.0837	0.42

*BUN, serum creatinine, 4-hour creatinine clearance, and calculated creatinine clearance models were adjusted for age, gender, BMI, work status (current vs. former lead worker), hypertension, diabetes, use of analgesics, and smoking status (current, ex, never). NAG and RBP models were adjusted for age, gender, BMI, work status, systolic blood pressure, diabetes, and smoking status. β coefficients and standard errors of the β coefficients for patella, blood, and tibia lead have been multiplied by 10^2 . The oldest tertile of workers is the reference group (denoted by ** after applicable age measure); the beta coefficient for this term is therefore the slope for the association between the lead variable and the renal outcome in the older workers. The slope in the younger age category (age cat 1 which is the youngest 67th percent) is obtained by adding the beta coefficient of the cross-product term (below the reference category) to the beta coefficient of the reference category (i.e., the slope for the association between patella lead and serum creatinine in the younger age group is $-0.000049 [0.000147 + -0.000196]$, p-values for the cross-product terms of age and lead measure reflect the statistical significance of the difference between the slopes of the regression line in the younger age category and the regression line for the oldest age group. $\dagger n = 574$ in models with tibia, since this lead biomarker was obtained in the second evaluation of the study.

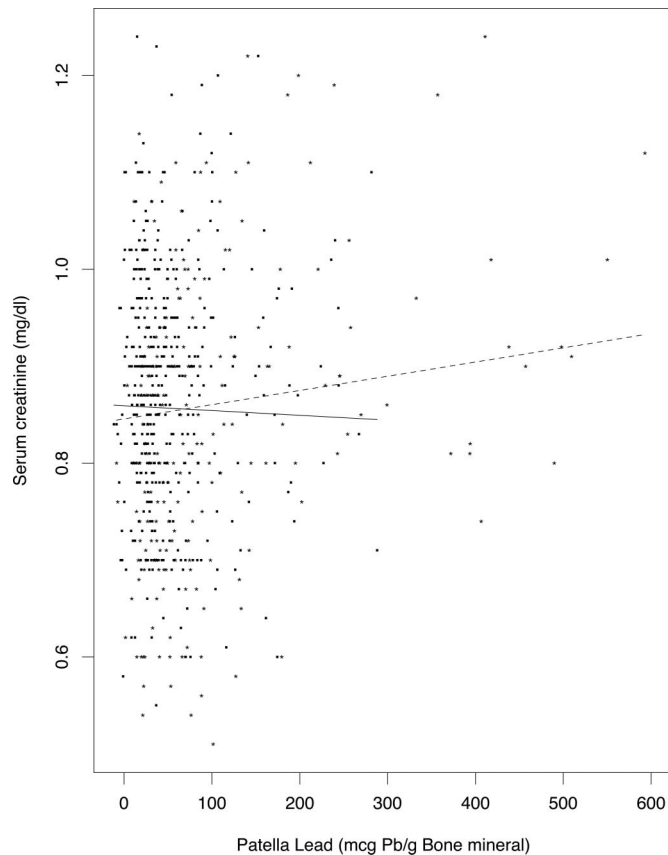


Fig. 1. Plot of model assessing effect modification by age (dichotomized at the 67th percentile) on the association between patella lead and serum creatinine in Korean lead workers. Actual data (with outliers removed) are plotted; asterisks represent participants in the older age range and squares represent participants in the younger age range. The dashed line is the regression line for the association between patella lead and serum creatinine in the older age group, following adjustment as shown in Table 5. The solid line represents the same association in the younger participants. These lines show the actual slopes (ie, are not multiplied by 100).

rean lead worker population provide further support for an age difference in direction of associations that is consistent with hyperfiltration.³ It must be noted, however, that hyperfiltration is an hypothesized but not established mechanism for lead-related nephrotoxicity at the current time. The differences in adverse renal outcomes by lead dose observed in the rodent studies cited previously^{19,20} suggest that similar initial hyperfiltration may not result in the same degree of renal impairment; other susceptibility factors may be involved. In this regard, lead exposure duration and dose were additional factors that varied in the human studies cited above. Thus, they may contribute to the observed differences. Interestingly, in our analyses, associations of blood lead and

renal outcomes were similar to those observed between bone lead (both cortical and trabecular) and renal outcomes. However, this was not the case in the other studies cited above, in which few blood lead associations were observed. This difference may be related to the high correlation of the lead biomarkers in our population.

In general, in the data reported herein, relations differ more by renal outcome than by lead measure. However, associations with DMSA-chelatable lead in models of clinical renal function are different from associations for the other three biomarkers. This is despite the fact that DMSA-chelatable lead also is highly correlated with the other lead measures. This biomarker is dependent on renal function and the collection

time was only 4 hours. Therefore, it is possible that the amount of lead that is excreted in this relatively short time period after chelation is influenced not only by bioavailable lead burden, but also by high-normal as well as actual supranormal glomerular filtration. This could potentially result in stronger inverse associations with this lead biomarker, particularly in the younger workers in whom high-normal and supranormal glomerular filtration are more common.

In conclusion, associations between patella lead and the renal outcomes were similar to associations between blood and tibia lead and renal outcomes. This may be the result of high correlations among the lead biomarkers in this population. In contrast, DMSA-chelatable lead associations with the clinical renal outcomes were different. This difference may be related, in part, to the influence of renal function on its measurement.

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