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Correlates of Bone and Blood Lead Levels among Middle-aged and Elderly Women

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In 1993–1995, the authors evaluated risk factors for elevated blood and bone lead levels in 264 Boston, Massachusetts, area women previously selected for a case-control study of lead and hypertension. Bone lead was measured at the tibia and patella with K x-ray fluorescence. Blood lead was analyzed by graphite furnace atomic absorption. Participants were aged 46–74 years and had mean lead levels of 3 (standard deviation, 2) µg/dl (blood), 13 (standard deviation, 9) µg/g (tibia), and 17 (standard deviation, 11) µg/g (patella). In multivariate linear regression models, use of postmenopausal estrogen (inverse) and alcohol intake (positive) were significantly associated with blood lead levels. Both bone lead measures were significantly and positively associated with blood lead but only among postmenopausal women not using estrogen; for example, an increase from the first to the fifth quintile of tibia lead level (19 µg/g) was associated with a 1.7-µg/dl increase in blood lead (p = 0.0001) in this group. Older age and lower parity were associated with higher tibia lead; only age was associated with patella lead. The observed interaction of bone lead with estrogen status in determining blood lead supports the hypothesis that increased bone resorption, as occurs postmenopausally because of decreased estrogen production, results in heightened release of bone lead stores into blood. *Am J Epidemiol* 2002;156: 335–43.

blood; bone and bones; estrogen replacement therapy; lead; menopause; nutrition

Abbreviation: NHS, Nurses' Health Study.

There is growing epidemiologic evidence that lead exposures previously thought to be without consequence are associated with the development of a variety of chronic disorders in adults, including impairment of renal, cardiovascular, and cognitive function (1–7). Although sources of lead pollution in the United States have declined substantially (8), this persistent environmental contaminant can still be found in water, soil, air, and food products. As a consequence, the general population has ongoing exposures to lead, with potentially adverse health consequences.

Most (95 percent) of the lead to which adults are exposed is sequestered in bone, with the remainder deposited in blood and other soft tissues. Lead in blood has a short half-life (30 days), whereas lead in bone has a half-life of up to 25 years (9). Lead deposits in bone can be resorbed and released to blood during normal bone remodeling, during periods of enhanced bone resorption as occur in certain disease states (hyperthyroidism, for example), and with the normal physiologic response to pregnancy, lactation, postmenopausal declines in estrogen, and aging (10–13). As a result, bone lead stores represent a potential source of soft-tissue lead exposure, even with declining environmental exposures.

Of the few studies evaluating determinants of bone lead in women, age, smoking, and breastfeeding (inverse association) have been identified as potential predictors of bone lead concentrations (14, 15). Understanding both the sources of lead deposition in bone and the factors contributing to bone lead retention or release is important to the development of strategies for minimizing lead's soft-tissue toxicities. Middle-aged and elderly women may be particularly at risk for bone

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lead release both because of hormonal and age-related changes in bone mineral metabolism and because their bone lead concentrations reflect higher lead exposures characteristic of previous decades. This study was undertaken to evaluate demographic, lifestyle, dietary, and reproductive risk factors for elevated blood and bone lead levels in middle-aged and elderly women. In addition, our goals included testing the hypothesis that use of exogenous estrogens modifies the relation between blood and bone lead levels.

MATERIALS AND METHODS

Study population

The Nurses' Health Study (NHS) is a prospective evaluation of chronic disease in a US sample of 121,700 female registered nurses (16). Since the study's initiation in 1976, biennial mailed questionnaires have been used to ascertain health outcomes, lifestyle, and dietary exposure measures among participants. Our study population was a subsample of the NHS cohort that had previously been evaluated in a case-control study of hypertension and lead exposure (7). Women were eligible for the case-control study if they lived in the greater Boston, Massachusetts, metropolitan area; did not have a history of major, chronic disease; and were not obese (body mass index (kg/m^2) ≥ 29). Women who remained free of major, chronic disease after 1990 were invited to participate as controls, and women who first reported a diagnosis of hypertension between 1990 and 1994 were invited to participate as cases. Controls were frequency matched to cases by 5-year age groups. Between 1993 and 1995, 301 Boston-area NHS participants agreed to and did complete this previous case-control study evaluation by attending our outpatient General Clinical Research Center, where additional measurements were made (see below). A final population of 264 women were included in the current analyses after we excluded 37 for whom at least one of the following covariates was missing: blood lead (n = 2), diet history from the 1990 NHS questionnaire (n = 20), smoking history (n = 3), and reproductive history (n = 12).

This study was approved by the Human Research Committee of Brigham and Women's Hospital in Boston. Written informed consent was obtained from each participant before the study evaluation was initiated.

Questionnaire

Every 2 years, NHS participants complete a mailed questionnaire requesting information about the development of a variety of diseases as well as on weight, medication and dietary supplement use, tobacco use, reproductive history, and, since 1980, detailed diet and alcohol intake histories. On the basis of the responses to the self-reported food frequency questions in this questionnaire, intake of nutrients has been validated in this population (17). When recruited for the case-control study, each participant updated her medication use and completed a questionnaire eliciting information about potential risk factors for lead exposure.

Medical evaluation

Height (in centimeters) and weight (in pounds (1 pound = 0.454 kg)) were measured with a wall-mounted stadiometer and digital scale.

Bone lead measurements

For each participant, bone lead measurements were made of the midtibial shaft (cortical bone) and patella (trabecular bone) by K x-ray fluorescence, a noninvasive technique for measuring skeletal lead content that can distinguish among very low lead burdens (18). A technical description and validity specifications of the ABIOMED instrument used for these measurements (ABIOMED, Inc., Danvers, Massachusetts) have been published elsewhere (18–20). This instrument provides an unbiased estimate of bone lead levels normalized to bone mineral content and expressed as micrograms of lead per gram of bone mineral (μg/g). The instrument also provides an estimate of the uncertainty for each measurement equivalent to the standard deviation of repeated measurements. Negative estimates of bone lead concentrations may occur for lead values close to zero. Use of all point estimates without imposition of a minimum detectable limit has been identified as the most appropriate method of using these data in epidemiologic studies (21).

Blood lead measurements

Samples for whole blood lead determination were collected in trace-metal-free tubes (with ethylenediaminetetraacetic acid) and were analyzed by ESA Laboratories, Inc. (Chelmsford, Massachusetts). The ESA protocol for blood lead analysis as well as quality control and quality assurance specifications are described elsewhere (5). In brief, well-mixed whole blood samples were diluted with a matrix modifier and were analyzed by Zeeman background-corrected flameless graphite furnace atomic absorption. The limit of detection for the blood lead concentrations was 1.0 μg/dl.

Statistical methods

Three lead measures were considered in these analyses: whole blood lead (μg/dl), patella lead (μg/g), and tibia lead (μg/g). Blood lead concentrations designated as less than the limit of detection (n = 17) were assigned a value of half the detection limit (0.5 μg/dl). For each lead variable, outliers were defined by using the extreme studentized deviate (ESD) procedure (22).

Self-reported intake according to the 1990 NHS food frequency questionnaire was used to estimate intake of alcohol (g/day) and calorie-adjusted nutrients (23). Body mass index was defined by using height and weight measures obtained at the study evaluation. Smoking, reproductive history, education, and physical activity (self-reported aerobic exercise and activities in metabolic equivalents per week) measures were obtained from the biennial NHS questionnaires.

Potential determinants of blood or bone lead concentrations identified in previous studies (14, 15, 24–27) were considered

TABLE 1. Characteristics† of participants in a study of determinants of body lead burden among middle-aged and elderly women, Boston, Massachusetts, area, 1993–1995

Characteristic	Participants included (*n* = 264)‡ (mean value (standard deviation))		Participants excluded (*n* = 37)§		
			Mean value (standard deviation)		No.¶
Age (years)	60.2 (7.2)		58.8 (7.2)		37
Body mass index (kg/m^2)	25.6 (3.4)		26.4 (3.6)		37
Alcohol intake (g/day)	6.8 (9.7)		4.3 (4.2)		17
Dietary calcium (mg/day)	966 (432)		1,048 (489)		17
Blood lead (µg/dl)	3 (2)		3.5 (2)		35
Tibia lead (µg/g)	13 (9)		15 (9)		37
Patella lead (µg/g)	17 (11)		18 (10)		37
	No.	%	No.	%	No.¶
Breastfed infant(s)	180	68	23	68	34
Postmenopausal estrogen use					
Premenopausal	41	16	1	3	
Current use	99	38	17	59	
Former use	44	17	5	17	
Never use	80	30	6	21	29
Pack-years of smoking					
0	97	37	14	41	
1–19	84	32	12	35	
20–39	42	16	4	12	
≥40	41	15	4	12	34
Hypertension	79	30	22*	59	37

* $p \leq 0.05$ (*t*-test comparison of means, Wilcoxon rank sum test for alcohol intake, chi-square comparison of proportions).

† Diet and alcohol variables were taken from the 1990 Nurses' Health Study (Am J Epidemiol 1986;123:894–900) questionnaire; nutrients were adjusted for total calorie intake.

‡ Data analyzed.

§ At least one key covariate was missing.

¶ Number of participants for whom values were not missing.

and included age, smoking, alcohol intake, specific nutrient intakes (calcium, zinc, iron, vitamin C, vitamin D), education, occupational or other activities (e.g., house painting) associated with lead exposure risk, and reproductive history (parity, lactation, menopausal status, age at menopause, use of postmenopausal estrogen replacement therapy). Menopause and estrogen-related variables were assessed further by dichotomizing their values to define recent (<5 years) menopause, recent estrogen use (<5 years since discontinued) among former users, and long-term estrogen use (≥5 years) among current users. Measures of body mass index and physical activity were also considered in analyses because of their association with bone mineralization, which is hypothesized to impact bone lead deposition (28).

A base model of predictors of each blood and bone lead measure was developed by using the a priori, most consistently demonstrated nonoccupational determinants: age, tobacco use, and alcohol intake. Since information concerning the association of adult lead exposure measures with other nonoccupational covariates is more limited, we tested the predictive power of these other variables by adding each, one at a time, to the base model. All of the variables that were significant ($p \leq 0.05$) in these analyses were added to the base model to construct a final multivariate regression model.

The independent role of bone lead in the determination of blood lead was assessed by adding each bone lead measure to the final models predicting blood lead. To test for effect modification by estrogen status, models of the hypothesized interaction of bone lead with menopausal status and postmenopausal estrogen use in the determination of blood lead were constructed as follows: Blood lead = intercept + $\beta_1(Ic)$ + $\beta_2(If)$ + $\beta_3(In)$ + $\beta_4(Ip \times \text{bone lead})$ + $\beta_5(Ic \times \text{bone lead})$ + $\beta_6(If \times \text{bone lead})$ + $\beta_7(In \times \text{bone lead})$ + (other covariates), where $Ip = 1$ if premenopausal (reference group), 0 otherwise; $Ic = 1$ if current postmenopausal estrogen user, 0 otherwise; $If = 1$ if former postmenopausal estrogen user, 0 otherwise; and $In = 1$ if never postmenopausal estrogen user, 0 otherwise

The final models were repeated by excluding, one at a time, non-Whites ($n = 3$), observations for which uncertainties regarding bone lead measurement were high (patella

TABLE 2. Mean (standard error) age-adjusted blood and bone lead concentrations in relation to age, smoking, reproductive history, and quantiles of nutrient† and alcohol intake in middle-aged and elderly women (*n* = 264), Boston, Massachusetts, area, 1993–1995

Variable	No. of women	Blood lead (µg/dl)	Tibia lead (µg/g)	Patella lead (µg/g)
Age (years)				
46–54	80	2.7 (0.3)	10.5 (1.0)	14.9 (1.2)
55–64	102	3.4 (0.2)	12.7 (0.9)	17.0 (1.1)
65–74	82	3.3 (0.3)*	16.4 (0.9)***	19.8 (1.2)***
Pack-years of smoking				
0	97	2.9 (0.2)	12.8 (0.9)	16.3 (1.1)
1–19	84	3.1 (0.3)	13.5 (1.0)	17.8 (1.2)
20–39	42	3.3 (0.4)	13.5 (1.3)	16.1 (1.7)
≥40	41	3.7 (0.4)*	13.2 (1.4)	19.3 (1.7)
Postmenopausal estrogen use				
Premenopausal	41	2.5 (0.4)	13.1 (1.6)	16.1 (2.0)
Current use	99	2.2 (0.2)	12.6 (0.9)	16.7 (1.1)
Former use	44	3.8 (0.3)	13.7 (1.4)	20.0 (1.8)
Never use	80	4.3 (0.2)***	13.7 (1.0)	17.0 (1.2)
No. of years since menopause				
Premenopausal	41	2.9 (0.5)	12.9 (1.7)	15.8 (2.2)
<5	30	3.5 (0.5)	12.4 (1.8)	15.5 (2.2)
≥5	186	3.2 (0.2)	13.5 (0.7)	18.0 (0.9)
Parity				
Nulliparous	14	2.8 (0.6)	21.3 (2.2)	21.6 (2.9)
1	8	3.8 (0.8)	22.6 (2.9)	19.7 (3.8)
2	68	3.1 (0.3)	12.5 (1.0)	17.3 (1.4)
3	80	3.2 (0.3)	11.9 (0.9)	15.4 (1.2)
≥4	94	3.2 (0.2)	12.8 (0.9)***	17.8 (1.1)
Lactation (months)				
Nulliparous	14	2.8 (0.6)	21.3 (2.3)	21.6 (2.9)
0	70	3.0 (0.3)	14.0 (1.0)	17.8 (1.3)
0.5–5	88	3.4 (0.2)	12.8 (0.9)	17.1 (1.2)
9–48	92	3.1 (0.2)	11.7 (0.9)***	16.2 (1.1)*

Table continues

uncertainty > 15 µg/g, $n = 1$; tibia uncertainty > 10 µg/g, $n = 19$), women taking thyroid medication ($n = 27$), women with a childhood history of eating lead paint or of lead poisoning ($n = 3$), premenopausal women ($n = 41$), and outlier lead levels. When dietary supplements were a potential source of nutrient intake, analyses were performed twice—once by using total intake of a specific nutrient (food plus dietary supplements) and again by using intake from food sources only. To assess potential bias that might have been introduced by the case-control design of the parent study, the final models were repeated after excluding hypertensive subjects ($n = 79$), women using thiazide diuretics ($n = 8$), and women using antihypertensive medications ($n = 47$).

RESULTS

Study population

Almost all (99 percent) of the 264 participants were White, with a mean age of 60 years and a range of 46–74 years at the time of the study evaluation. Consistent with this age distribution, most (84 percent) participants were postmenopausal. There were relatively few current smokers (10 percent) and nulliparous women (5 percent).

The 37 women excluded from this analysis because at least one key covariate was missing were more likely to have hypertension than were participants for whom covariates were not missing (59 vs. 30 percent, $p = 0.001$) (table 1). Otherwise, there were no significant demographic, nutrient intake, or reproductive history differences between women included or excluded from the current analysis.

Bone and blood lead levels

Blood lead levels in this population were low, with a mean of 3 (standard deviation, 2) µg/dl and range of <1–14 µg/dl. Mean tibia and patella lead levels were 13 (standard deviation, 9) and 17 (standard deviation, 11) µg/g and ranged from –5 to 69 µg/dl and –5 to 87 µg/g, respectively.

TABLE 2. Continued

Variable	No. of women	Blood lead (μg/dl)	Tibia lead (μg/g)	Patella lead (μg/g)
Calcium (mg/day)				
321–600	52	3.7 (0.3)	13.9 (1.2)	18.0 (1.5)
605–754	53	3.1 (0.3)	13.5 (1.2)	15.8 (1.5)
756–971	53	3.4 (0.3)	13.4 (1.2)	18.6 (1.5)
972–1,267	53	2.7 (0.3)	13.0 (1.2)	17.7 (1.5)
1,268–2,583	53	2.9 (0.3)*	12.2 (1.2)	16.0 (1.5)
Vitamin C (mg/day)				
27–106	53	3.7 (0.3)	12.7 (1.2)	15.6 (1.5)
107–141	52	3.5 (0.3)	14.9 (1.2)	18.6 (1.5)
143–189	54	2.9 (0.3)	13.5 (1.2)	17.9 (1.5)
191–263	52	3.0 (0.3)	12.7 (1.2)	17.4 (1.5)
266–1,534	53	2.7 (0.3)**	12.2 (1.2)	16.6 (1.5)
1990 alcohol intake (g/day)				
0	71	2.5 (0.3)	11.6 (1.0)	16.8 (1.3)
0.9–2.9	64	2.8 (0.3)	12.3 (1.1)	15.7 (1.3)
3.0–10.6	65	3.5 (0.3)	14.5 (1.1)	16.3 (1.3)
10.7–62.5	64	4.0 (0.3)***	14.6 (1.1)**	20.1 (1.4)**
1990 wine intake (g/day)				
0	96	2.7 (0.2)	11.8 (0.9)	17.0 (1.1)
0.8	47	3.1 (0.3)	12.4 (1.2)	16.5 (1.6)
1.5–3.1	56	2.8 (0.3)	13.5 (1.1)	15.1 (1.5)
4.7–49.5	65	4.2 (0.3)***	15.6 (1.1)***	19.8 (1.3)*
1990 liquor intake (g/day)				
0	151	2.8 (0.2)	12.4 (0.7)	17.2 (0.9)
1.0	38	3.0 (0.4)	13.4 (1.4)	15.6 (1.8)
2.0–6.0	39	4.0 (0.4)	14.7 (1.4)	16.6 (1.7)
11.2–35.0	36	3.7 (0.4)*	14.6 (1.4)	19.6 (1.8)

* $p \leq 0.15$; ** $p \leq 0.05$; *** $p \leq 0.01$ (*p* for trend).

† Nutrient intakes are self-reported total dietary intake (food plus dietary supplements) from the 1990 Nurses' Health Study (Am J Epidemiol 1986;123:894–900) questionnaire; nutrients were adjusted for total calorie intake.

Correlates of tibia and patella lead

Both tibia and patella lead levels increased with age and with alcohol intake, particularly wine (table 2). Associations of bone lead levels with reproductive history were less consistent; for example, in age-adjusted analyses, tibia but not patella lead concentrations decreased significantly with increasing parity and lactation (table 2). Neither bone lead measure appeared to be related to estrogen use, smoking, body mass index, physical activity, education (registered nurse's, bachelor's, or ≥master's degree), or recent occupation (nursing, nonnursing, or retired). Furthermore, no consistent or significant associations of tibia or patella lead levels with nutrient intake were found in these data (table 2), including measures of zinc, iron, or vitamin D intake (data not shown). Use of micronutrient intake from food alone (compared with use of total dietary intake, including supplements) and use of a long-term dietary measure (mean nutrient intake from the 1980–1990 NHS questionnaires) gave similar results.

Parity and lactation were significant ($p \leq 0.05$) correlates of tibia lead when added to the base linear regression model that included age, smoking, and alcohol. When both parity and lactation were included in the final model for tibia lead, only parity retained statistical significance (table 3). There were no significant correlates of patella lead beyond those represented in the base model. Thus, in the final models, age and parity were significantly associated with tibia lead, and age alone was significantly associated with patella lead (table 3). Specifically, with each year of a woman's age, tibia and patella lead levels increased by 0.3 μg/g and 0.2 μg/g, respectively (table 3). Multiparous women had tibia lead levels that were approximately 7 μg/g lower than the levels in nulliparous women (table 3).

Correlates of blood lead

In age-adjusted analyses, blood lead concentrations were higher in postmenopausal women not using estrogen than in postmenopausal women using estrogen or in premenopausal

TABLE 3. Final linear regression models (covariate: beta (standard error)) of determinants of blood and bone lead concentrations among a sample of middle-aged and elderly women (n = 264), Boston, Massachusetts, area, 1993–1995

Outcome	Blood lead (μg/dl)	Blood lead (μg/dl)	Blood lead (μg/dl)	Tibia lead (μg/g)	Patella lead (μg/g)
Intercept	2.39 (1.24)*	3.52 (1.25)***	2.90 (1.20)**	2.25 (5.55)	1.59 (5.96)
Age (years)	–0.01 (0.02)	–0.03 (0.02)	–0.02 (0.02)	0.28 (0.08)***	0.24 (0.10)**
Pack-years of smoking					
0	0	0	0	0	0
1–19	0.08 (0.31)	0.11 (0.30)	–0.01 (0.30)	0.10 (1.26)	1.49 (1.63)
20–39	0.04 (0.39)	0.05 (0.37)	0.11 (0.37)	–0.35 (1.59)	–0.78 (2.03)
≥40	0.34 (0.40)	0.40 (0.38)	0.26 (0.39)	0.24 (1.62)	2.40 (2.09)
1990 alcohol intake (g/day)					
0	0	0	0	0	0
0.9–2.9	0.43 (0.36)	0.44 (0.35)	0.45 (0.34)	0.54 (1.45)	–1.32 (1.88)
3.0–10.6	1.07 (0.36)***	0.83 (0.35)**	1.01 (0.35)***	2.24 (1.46)*	–0.68 (1.89)
10.7–62.5	1.45 (0.36)***	1.24 (0.35)***	1.20 (0.35)***	2.44 (1.49)*	3.12 (1.90)*
Postmenopausal estrogen use					
Premenopausal	0	0	0		
Current use	–0.46 (0.44)	–0.19 (0.44)	–0.30 (0.43)		
Former use	1.19 (0.57)**	1.37 (0.56)**	1.16 (0.56)**		
Never use	1.66 (0.48)***	1.82 (0.47)***	1.81 (0.46)***		
Parity					
0				0	
1				3.21 (3.81)	
2				–6.64 (2.69)**	
≥3				–6.83 (2.52)***	
Breastfed infant(s)				–1.75 (1.20)*	
Tibia lead (μg/g)					
Premenopausal		–0.006 (0.03)			
Current ERT†		0.05 (0.03)*			
Former ERT		0.08 (0.02)***			
Never ERT		0.11 (0.03)***			
Patella lead (μg/g)					
Premenopausal			–0.01 (0.03)		
Current ERT			0.03 (0.02)		
Past ERT			0.06 (0.02)***		
Never ERT			0.10 (0.02)***		
Model R^2	0.23	0.30	0.31	0.16	0.07

* $p < 0.15$; ** $p \leq 0.05$; *** $p < 0.01$.
† ERT, estrogen replacement therapy.

women (table 2). Blood lead levels did not differ significantly between long-term (≥5 years) and short-term (<5 years) estrogen users, nor was mean blood lead level in former estrogen users significantly affected by time since last use, although there were only 16 former users who last used estrogen within 5 years of the study.

Blood lead levels increased with alcohol intake; this association was generally consistent among alcoholic beverages (wine, liquor, and beer) but was most significant for wine (table 2). A consistent and significant ($p \leq 0.05$) linear trend of decreasing blood lead with increasing intake was found for vitamin C (table 2), but blood lead was unrelated to intake of other nutrients including zinc, iron, and vitamin D (data not shown). Similar results were found in analyses using nutrient intake from food alone (excluding supplements) or the mean of total nutrient intake from the 1980–1990 NHS questionnaires.

In multivariate linear regression models adjusted for age, smoking, and alcohol, use of postmenopausal estrogen replacement therapy was a significant ($p \leq 0.05$) correlate of

blood lead (table 3). Both patella and tibia lead were independently associated with blood lead, but this effect was modified by estrogen status. Specifically, among postmenopausal women who were former or never users of postmenopausal estrogen, an increase from the first to the fifth quintile of tibia (19 μg/g) or patella (23 μg/g) lead concentration was associated with 1.7- and 1.8-μg/dl increases in blood lead, respectively. Patella and tibia lead were not significantly associated with blood lead levels among premenopausal women or postmenopausal women using estrogens (table 3, figure 1).

For all final models, one-at-a-time exclusion of non-Whites, observations in which uncertainty regarding patella or tibia lead measurement was high, hypertensive subjects, women using thiazide diuretics, women using antihypertensive medications, women taking thyroid medication, women with a childhood history of eating lead paint or of lead poisoning, premenopausal women, or outlier blood, tibia, or patella lead levels did not materially alter the results except in two cases. Although similar in magnitude, the relation of age with patella lead was no longer statistically significant after we excluded 79 women with hypertension. In addition, the magnitude and significance of the inverse relation of tibia lead with parity were diminished after seven outlier tibia lead values were excluded.

DISCUSSION

This is among the first studies to assess the relation of exogenous estrogen replacement and bone lead levels with blood lead levels in postmenopausal women. It has been hypothesized that increased bone resorption attributable to estrogen decline at menopause will result in bone lead release into the blood. Indirect support for this hypothesis has come from observational studies' findings of higher blood lead levels in post- than in premenopausal women (10, 29–31) and lower blood lead levels in postmenopausal women taking estrogen than in those not taking estrogen (24). Similarly, in our data, postmenopausal women who were not taking estrogens had higher blood lead levels than did either premenopausal women or postmenopausal women who were using estrogens (tables 2 and 3). Our results provide further support for this hypothesis by demonstrating an interaction of bone lead with estrogen status in the determination of blood lead; specifically, bone lead was positively associated with blood lead among only postmenopausal women who were not using estrogens (table 3, figure 1). Conversely, bone lead was not associated with blood lead among premenopausal women nor among postmenopausal women using estrogen replacement therapy (table 3, figure 1). These findings were similar for both patella (trabecular) and tibia (cortical) bone lead measures (table 3). Although trabecular bone is generally more sensitive than cortical bone to declines in estrogen, approximately 80 percent of the adult skeleton is cortical bone (32); both bone lead measures' estrogen-related contribution to blood lead may be a result of these properties.

In addition to a role for menopausal status, previous studies have demonstrated that smoking, alcohol intake, urban residence, education, income, and hematocrit are important determinants of blood lead levels in nonoccupationally exposed women (10, 24, 31, 33). Similar factors (plus race, dietary vitamin C, and dietary iron) have been found to be important determinants of blood lead in non-occupationally-exposed men (25, 26). The current study's participants were Boston-area registered nurses who were relatively homogeneous with regard to several risk factors for lead exposure, including smoking, education, occupation, and race. For example, most (90 percent) of the women were nonsmokers at the time of the study. Consistent with this risk profile, blood lead levels in the study population were lower than levels observed in most other populations of women evaluated for risk factors associated with increased blood lead, for whom mean blood lead levels have ranged from approximately 3 to 12 μg/dl (10, 14, 24, 29, 31).

Relative homogeneity with regard to lead exposure risks and low lead levels may explain the lack of association of some previously identified risk factors with lead measures in this analysis (table 2). For example, although a correlate of blood lead in general populations with higher lead levels (33), smoking was not associated with lead measures in this study. Indeed, in a recent population-based study of 109 Danish women with similar blood lead levels (mean, 3 μg/dl), smoking was not significantly associated with blood lead (29).

Alternatively, small sample size may in part explain the lack of association of blood or bone lead with some previously identified risk factors. For example, in post hoc power calculations based on previously reported associations of lead measures with smoking (25), we had less than 65 percent power to detect associations of smoking with blood or bone lead levels.

In our study, parity was inversely associated with tibia lead (tables 2 and 3), consistent with reproductive correlates of bone lead observed among women (including middle-aged women) studied elsewhere (14) and hypothesized to result from relative increases in bone resorption during pregnancy and lactation because of increased calcium requirements. Given that participants' parity preceded their bone lead measures by many years, the longer half-life of tibia versus patella lead (34) may partly explain the lack of a significant parity association with patella lead. Furthermore, we did not find monotonic declines in tibia lead with increasing parity; instead, after adjustment for age and other covariates, women with two or more children had approximately 7-μg/g lower tibia lead levels than nulliparous women did (table 3). In these cross-sectional analyses, it was impossible to distinguish the direction of this association—for example, whether it was the result of parity-related declines in bone lead or lead-associated declines in fecundity. Nevertheless, the interpretation that these results reflect parity-related declines in bone lead are consistent with kinetic studies demonstrating that pregnancy is associated with a marked increase in the mobilization of lead from bone (13).

In multivariate analyses, neither blood nor bone lead measures were significantly associated with dietary intake of micronutrients. However, alcohol intake, particularly wine intake, was positively associated with blood lead (tables 2 and 3). In the context of our relatively homogeneous study

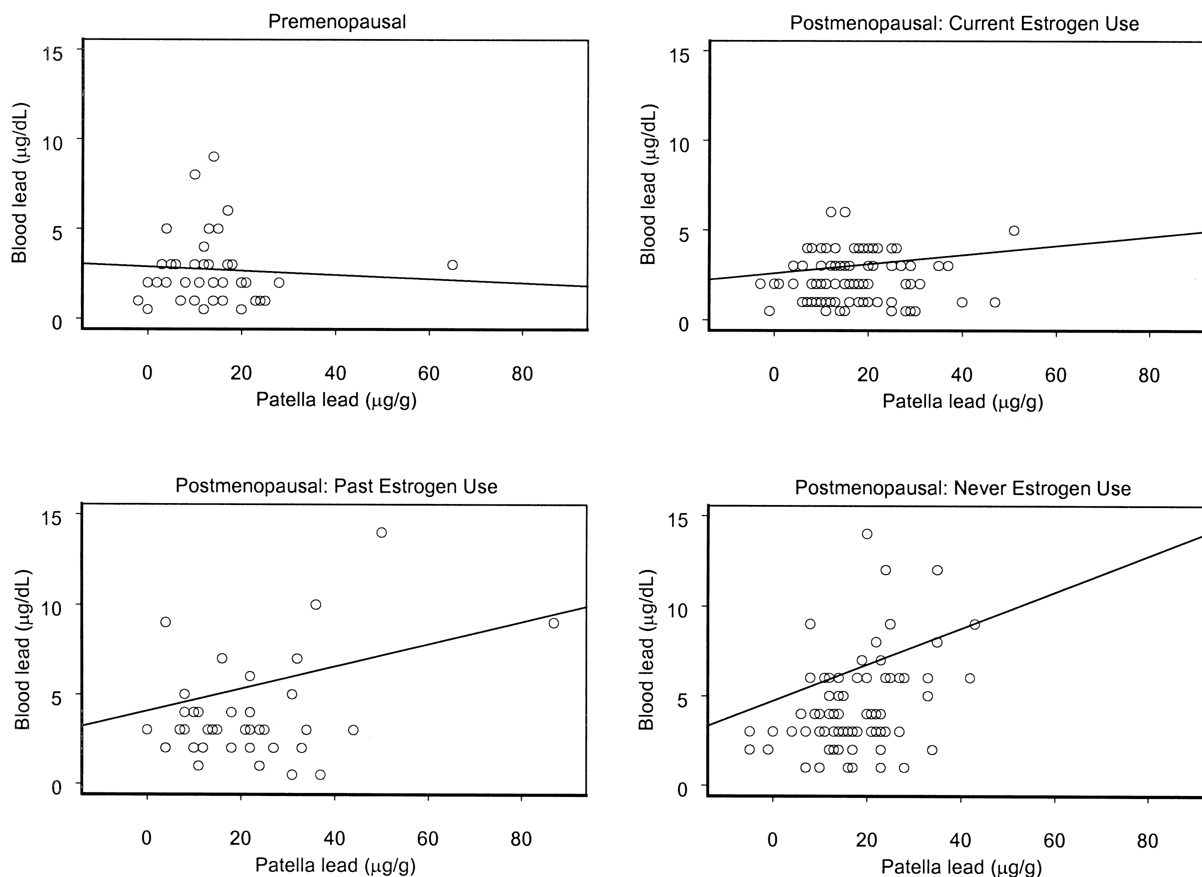

FIGURE 1. Relation of patella lead to blood lead level in a sample of middle-aged and elderly women (*n* = 264) in the Boston, Massachusetts, area, 1993–1995. Associations were adjusted for age, smoking, and alcohol intake and were stratified by menopausal status and, for postmenopausal women, estrogen use. dL, dl.

sample with low blood lead levels, it is notable that the primary environmental correlate of blood lead concentration was alcohol intake. In other studies (24, 29, 33), alcohol (particularly wine) has been associated with increased blood lead and represents a potentially modifiable exposure risk factor from both the perspective of lifestyle choices and that of regulatory intervention. For example, the use of tin-coated lead-foil cork capsules (35) (banned in the United States in 1996) and materials used in the production or storage of some wines can result in lead contamination (36).

Interpretation of the study findings includes consideration of the fact that the study population was originally identified as part of a case-control study of lead and hypertension. However, exclusion of women with hypertension or using antihypertensive medications did not materially alter our findings. The cross-sectional design is another limitation that precludes identifying the direction of associations.

Despite these limitations, our study findings support a potentially important role of estrogens (both endogenous and exogenous) in mitigating against bone lead release to blood. Evidence suggests that the more bioavailable fraction of blood lead (serum lead) is better correlated with bone than with whole blood lead (37, 38). As a consequence, lead exposures originating from bone stores may be toxicologically more important than realized previously. In the few instances in which it has been studied, bone lead appears to be a sensitive predictor of lead-associated risk of hypertension among women with low-level lead exposures (7). Whether bone lead is associated with the risk of other aging-associated chronic diseases such as neurocognitive disorders remains to be determined. Peri- and postmenopausal women may be particularly susceptible to lead toxicities related to bone lead release, and identification of potentially modifiable factors that prevent bone lead release may be useful for managing the potential health risks of chronic lead exposure in this population.

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