Lead and Hypertension in a Sample of Middle-Aged Women

Susan A. Korrick, MD, MPH, David J. Hunter, MBBS, ScD, Andrea Rotnitzky, PhD, Howard Hu, MD, MPH, ScD, and Frank E. Speizer, MD

ABSTRACT

Objectives. The role of lead exposure as a risk factor for hypertension is less well defined among women than among men. This case–control study assessed the relation of blood and bone lead concentrations to hypertension in women.

Methods. Cases and controls were a subsample of women from the Nurses' Health Study. Hypertension was defined as a physician diagnosis of hypertension between 1988 and 1994 or measured systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg.

Results. Mean (SD) blood lead concentration was 0.15 (0.11) μmol/L; mean tibia and patella lead concentrations by K-x-ray fluorescence were 13.3 (9.0) and 17.3 (11.1) μg/g, respectively. After adjustment for potentially confounding factors, an increase from the 10th to the 90th percentile of patella lead values (25 μg/g) was associated with approximately 2-fold (95% confidence interval = 1.1, 3.2) increased risk of hypertension. There was no association between hypertension and either blood or tibia lead concentrations.

Conclusions. These findings support a potentially important role for low-level lead exposure as a risk factor for hypertension among non–occupationally exposed women. (*Am J Public Health*. 1999;89:330–335)

High blood pressure is a major contributor to the US population's morbidity and mortality from hypertension and related conditions such as coronary artery disease, stroke, and renal insufficiency.[1] Remediable causes are identified for fewer than 5% of individuals with hypertension.[2] Despite considerable evidence from both animal models[3–5] and epidemiologic studies[6–10] that low-level lead exposure is related to increases in blood pressure, acceptance of this association remains controversial.[11] The mechanism of this association is unknown; it has been observed in the absence of lead-associated renal disease and at blood lead concentrations previously believed to be nontoxic in adults.

Much of the epidemiologic evidence supporting this relationship has been derived from studies of male subjects.[7–10] Studies with female participants have found a less consistent association between lead and blood pressure. In particular, the association in women appears to be sensitive to the variables included in the statistical models and may vary according to age,[12] alcohol use,[13–15] and other factors.[6,16,17] When a relation between lead and blood pressure has been observed, results from both animal models and epidemiologic studies were consistent with a weaker effect in women than in men.[17,18]

With one exception, a study of men,[7] studies of this association have relied on blood lead concentration as a measure of exposure. However, blood lead concentrations reflect short-term (half-life of 30 days) lead exposures. Most (95%) adult lead stores are in bone and have been hypothesized to be better determinants of chronic lead toxicities because they reflect long-term exposure (half-life of years to decades).[19,20] Furthermore, the more bioavailable fraction of blood lead (plasma lead) has been hypothesized to correlate better with bone than with whole blood lead concentrations.[21] Because the possible role of lead exposure as a risk factor for hypertension is less well defined among women than among men, evaluation of the association of bone lead stores and hypertension in women is particularly valuable.

Methods

Study Population

Our study population was a subsample of Boston-area women in the Nurses' Health Study (NHS), a prospective evaluation of chronic disease in a national sample of 121 700 female registered nurses that was initiated in 1976.[22] Biennial mailed questionnaires were used to ascertain health outcomes, lifestyle, and dietary exposure measures among participants. At the time of the current study (July 1993 to July 1995), 5621 active NHS participants resided in the Boston metropolitan area. Of these women, 402 (7%) first reported a physician's diag-

Susan A. Korrick, David J. Hunter, Howard Hu, and Frank E. Speizer are with the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston. Susan A. Korrick, Howard Hu, and Frank E. Speizer are also with the Department of Environmental Health, Harvard School of Public Health, Boston. David J. Hunter is also with the Department of Epidemiology, Harvard School of Public Health. Andrea Rotnitzky is with the Department of Biostatistics, Harvard School of Public Health.

Correspondence and requests for reprints should be sent to Susan A. Korrick, MD, MPH, Channing Laboratory, 181 Longwood Ave, Boston, MA 02115 (e-mail: susan.korrick@channing.harvard.edu).

This paper was accepted August 24, 1998.

Note. The contents of this paper are the sole responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health or the Environmental Protection Agency.

nosis of hypertension on the NHS questionnaire in 1990, 1992, or 1994.

Potential controls were excluded from the study if they had a history of hypertension or other major chronic disease (cardiovascular disease, renal disease, diabetes, malignancies), use of antihypertensive or hypoglycemic medication, or obesity (body mass index [BMI] ≥ 29 kg/m^2). Similarly, hypertensive women reporting cardiovascular disease, renal disease, diabetes, or malignancies; medication use; or obesity before 1990 were excluded from the study.

From the eligible controls, women were selected by a stratified randomization scheme to obtain approximately equal numbers of women with self-reported blood pressure in the low normal range (systolic <115 mm Hg and diastolic <75 mm Hg) and in the high normal range (systolic >134 and <140 mm Hg or diastolic >84 and <90 mm Hg). Up to 4 controls were matched by 5-year age groups to each eligible case. A final sample of 214 cases and 475 controls (total n = 689) were identified as eligible and invited to attend our Clinical Research Center, where additional measurements were made (see below).

This study was approved by the Human Research Committee of the Brigham and Women's Hospital.

Questionnaires

Every 2 years, NHS participants complete a mailed questionnaire requesting information about the development of a variety of diseases including hypertension and about weight, medication and dietary supplement use, tobacco use, reproductive history, and, since 1980, detailed history of alcohol use and diet.

When recruited for the current case–control study, each participant updated her status by a mailed questionnaire regarding a history of hypertension and the use of antihypertensive medications.

Medical Evaluation

At the beginning of the study visit, right arm systolic and fifth-phase diastolic blood pressure were measured with the participant seated in a quiet room after a 5-minute rest. Measurements were taken with a random zero sphygmomanometer by a researcher certified in the use of a standard blood pressure measurement protocol described in detail elsewhere.[23] The mean of 3 measurements was used to estimate each participant's systolic and diastolic blood pressures. Standard blood tests, including a complete blood count and serum creatinine, were performed.

Bone Lead Measurements

Each participant had bone lead measurements from the midtibial shaft and patella by K-x-ray fluorescence, a noninvasive technique for measuring skeletal lead content that can distinguish among very low lead burdens.[24] A technical description and validity specifications of the ABIOMED (ABIOMED Inc, Danvers, Mass) instrument used for these measurements have been published elsewhere.[24,25] This instrument provides an unbiased estimate of bone lead levels (normalized to bone mineral content as micrograms of lead per gram of bone mineral) and an estimate of the uncertainty of each measurement. Estimates of bone lead concentrations may be negative for lead values close to zero. The technicians measuring bone lead were blinded to the participant's case–control status.

Blood Lead Measurements

Samples for whole blood lead determination were collected in trace metal–free tubes (with ethylenediaminetetraacetic acid) and analyzed by ESA Laboratories, Inc (Chelmsford, Mass). The ESA blood lead analysis protocol and quality control and quality assurance specifications are described elsewhere.[7] In brief, well-mixed whole blood samples were diluted with a matrix modifier and analyzed by Zeeman background-corrected flameless graphite furnace atomic absorption. The detection limit for blood lead concentrations was 0.048 μmol/L (1.0 μg/dL).

Statistical Methods

Three lead exposure variables were considered in these analyses: whole blood lead (μmol/L), patella lead (μg/g), and tibia lead (μg/g). Blood lead concentrations designated as less than the detection limit were assigned a value of half the detection limit (0.024 μmol/L [0.5 μg/dL]). For each lead variable, outliers were identified as values greater than 3 interquartile ranges beyond the first or third quartile of the distribution from a box plot display of values.

These analyses include the cases and controls with disease status confirmed by history and measured blood pressure at the study evaluation. Cases were women with a self-reported history of physician-diagnosed hypertension or measured systolic blood pressure ≥ 140 mm Hg or measured diastolic blood pressure ≥ 90 mm Hg. The controls whose measured blood pressure did not fit into high and low normal ranges were divided at their median blood pressure (121/75 mm Hg)—those with measured systolic or diastolic blood pressure above this value were grouped with the high normal range controls (n = 53), and the remainder were classified as low normal range controls (n = 25). Cases reporting a physician's first diagnosis of hypertension before 1988 on the updated medical history questionnaire were excluded (n = 4).

Alcohol consumption (g/day), dietary calcium and sodium (mg/day) intakes adjusted for total calorie intake, and BMI (weight/height^2 in kg/m^2) were defined in terms of the mean of nonmissing values from the 3 most recent NHS questionnaires obtained between 1980 and 1986; thus, these data were recorded before 1988 when the first cases of hypertension were diagnosed. Smoking status (current, former, never) was defined by the nonmissing information from the 1990, 1992, or 1994 NHS questionnaire that was administered closest to the time of each woman's study evaluation. Menopausal status was defined by information from the 1992 or 1994 NHS questionnaire that was administered closest to the time of each woman's evaluation. Information about job status (nursing, retired, nonnursing/homemaker) was obtained from the 1992 NHS questionnaire.

Ordinal regression modeling[26] to assess the relation between lead exposure variables and the odds of hypertension in the study population used the 3 blood pressure categories (hypertension, high normal, low normal). Specifically, a proportional odds model (PROC LOGISTIC, Statistical Analysis System, SAS Institute Inc, Cary, NC) was used to calculate the odds of being (1) a case vs the combined control groups and (2) a combined case and high normal control group vs the low normal control group as a function of lead exposure. A χ^2 score statistic was used to test the homogeneity of the 2 disease-exposure odds ratios; if they were homogeneous, a single odds ratio was reported. Potential confounders of the relation between lead and hypertension included in an initial model were age, dietary calcium intake, alcohol intake, smoking status, dietary sodium intake, BMI, and family history of hypertension (in a parent or sibling). The matched design was accounted for by including age as a continuous variable in all models.[27]

To assess effect modification by alcohol intake, age, and menopausal status, a Wald χ^2 test for interaction between patella lead and each variable was used. Women in the 80th percentile of alcohol consumption or above were compared with all others, age was dichotomized at 55 years as per results of previous studies,[12] and postmenopausal and premenopausal women were compared.

TABLE 1—Selected Characteristics of Study Population and Eligible Nonparticipants in a Study of Lead and Hypertension in Middle-Aged Women

	Study Population (n = 284)	Nonparticipants (n = 405)	P[a]
	Mean (SD)	Mean (SD)	
Age, y[b]	58.7 (7.2)	58.4 (7.1)	.62
BMI, kg/m^2	22.9 (2.3)	23.2 (2.5)	.09
Diet Ca^{++}, mg/day	916 (331)	846 (304)	.005
Diet Na^{+}, mg/day	1833 (383)	1881 (437)	.13
Alcohol, g/day	8.5 (10.4)	8.5 (10.5)	.96
	n (%)	n (%)	
Family hypertension	155 (55)	186 (46)	.03
Smoking status			
Current	16 (6)	19 (5)	.31
Former	162 (57)	252 (62)	
Never	106 (37)	130 (32)	
Job status[c]			
Nursing	162 (59)	214 (56)	.80
Retired	66 (24)	99 (26)	
Nonnursing[d]	48 (17)	67 (18)	
Hypertension status			
Case[e]	85 (30)	129 (32)	.04
Control			
Low[f]	115 (40)	127 (31)	
High[g]	84 (30)	149 (37)	

Note. BMI = body mass index.
[a]*t*-test comparison of means; χ^2 test comparison of proportions.
[b]Age as of January 1, 1993.
[c]Only 276 participants and 380 nonparticipants had job status information.
[d]Includes homemakers.
[e]Self-reported physician-diagnosed hypertension from the Nurses' Health Study questionnaire.
[f]Self-reported usual blood pressure: systolic <115 mm Hg and diastolic <75 mm Hg.
[g]Self-reported usual blood pressure: systolic >134 mm Hg and/or diastolic >84 mm Hg.

The untransformed and the natural logarithm (ln) transformed values for each lead variable were used in the logistic regression analyses because of evidence from other studies that incremental increases in blood lead are associated with progressively smaller increases in blood pressure.[28] Because of a few negative values, bone lead concentrations were ln transformed after a constant, k, was added to each value. The value for k was chosen such that ln(bone lead + k) was approximately normally distributed.

Each lead exposure variable (blood lead, patella lead, and tibia lead) was considered separately in the initial models. Then all 3 lead exposure variables were considered simultaneously, and a final model was selected by a backward elimination procedure, retaining variables with $P \leq .05$.

Results

Study Population

Of the 689 eligible and age-matched Boston area women, 297 (43%) agreed to participate; completed study evaluations between 1993 and 1995; and, for cases, were first diagnosed with hypertension between 1988 and 1994 or had elevated blood pressure measured at their study evaluation.

These 297 participants included 93 cases and 204 controls identified by medical histories from the NHS questionnaires. Of the 93 cases, 73 (78%) corroborated a history of physician-diagnosed hypertension and/or had elevated blood pressure at the study visit. The remaining 20 cases were reclassified as controls. Of the 204 controls, 180 (88%) corroborated no history of physician-diagnosed hypertension and had normal blood pressure at their study visit. The remaining 24 controls with elevated blood pressure or recently diagnosed hypertension were reclassified as cases, leaving 97 cases and 200 controls for study. Eighty-nine of the 97 cases and 195 of the 200 controls had complete covariates available for the analyses, leaving a final study population of 284 women ranging in age from 47 to 74 years.

Women participating in the evaluation had higher dietary calcium intakes and were more likely to have a family history of hypertension than eligible nonparticipants (Table 1). There was some differential participation by blood pressure group (Table 1). Although there was no overall difference between participants' and nonparticipants' alcohol consumption (Table 1), participating cases consumed less alcohol than nonparticipating cases (7.1 g/day vs 10.2 g/day, $P = .03$), whereas participating controls consumed more alcohol than nonparticipating controls (9.1 g/day vs 7.8 g/day, $P = .16$). Otherwise, the results of comparisons of participants with nonparticipants were unchanged when cases and controls were analyzed separately.

Despite the use of prospective dietary and alcohol information, cases had lower dietary sodium and alcohol intakes than controls, although this difference was not significant in all comparisons (Table 2). Cases were more likely to have a family history of hypertension, to be postmenopausal, to have smoked, and to be retired or in a nonnursing job (including homemaker). Otherwise, high normal controls did not differ significantly from cases, whereas low normal controls were younger and thinner than cases.

Bone and Blood Lead Levels

Mean tibia and patella lead levels for cases and controls combined were 13.3 (9.0) μg/g and 17.3 (11.1) μg/g, with ranges from −5 to 69 μg/g and −5 to 87 μg/g, respectively. Blood lead levels were low, ranging from <0.05 to 0.68 μmol/L (<1 to 14 μg/dL) and a mean (SD) of 0.15 (0.11) μmol/L (3 [2] μg/dL).

Bone and Blood Lead Levels and Hypertension

In multivariate ordinal regression models evaluating one lead variable at a time, patella lead was associated with increased odds of hypertension ($P = .03$) (Table 3). In a final model derived from backward elimination of the model containing all covariates, including all 3 lead variables, patella lead was the only lead variable retained. An increase from the 10th to the 90th percentile of patella lead concentration (from 6 to 31 μg/g bone lead, a 25 μg/g increase) was associated with increased odds of hypertension of 1.86 (95% confidence interval = 1.09, 3.19) after adjustment for age, BMI, dietary sodium intake, and a family history of hypertension (Table 4), equivalent to the increased odds of hypertension associated with a 4 kg/m^2 increase in BMI in the final model. Exclusion, one at a time, of non-Whites (n = 3), outlier patella lead concentrations (n = 2), patella lead values with measurement uncertainty >15 (n = 1), cases with hypertension diagnosed

TABLE 2—Selected Characteristics of Cases with Hypertension and Controls in a Study of Lead and Hypertension in Middle-Aged Women

	Cases (n = 89)	High Controls (n = 73)		Low Controls (n = 122)	
	Mean (SD)	Mean (SD)	P^a	Mean (SD)	P^a
Age, y	61.1 (7.1)	61.1 (7.2)	.98	58.7 (7.1)	.02
BMI, kg/m^2	23.4 (2.4)	23.1 (2.4)	.47	22.5 (2.1)	.004
Diet Ca^{++}, mg/day	937 (383)	894 (323)	.46	913 (294)	.63
Diet Na^+, mg/day	1771 (381)	1815 (390)	.46	1887 (376)	.03
Alcohol, g/day	6.9 (9.4)	10.3 (11.9)	.05	8.7 (10.0)	.20
Blood lead, μmol/L	0.15 (0.11)	0.17 (0.12)	.37	0.15 (0.10)	.62
Tibia lead, μg/g	13.0 (9.4)	14.7 (10.0)	.27	12.7 (8.1)	.80
Patella lead, μg/g	19.5 (12.9)	17.2 (9.0)	.18	15.8 (10.6)	.03
Systolic BP, mm Hg	130 (15)	125 (8)	.01	106 (9)	.0001
Diastolic BP, mm Hg	76 (11)	77 (6)	.22	66 (6)	.0001
	n (%)	n (%)	P^a	n (%)	P^a
Family hypertension	57 (64)	44 (60)	.62	54 (44)	.004
White	87 (98)	73 (100)	NA[b]	121 (99)	NA[b]
Smoking status					
Current	5 (6)	1 (1)	NA[b]	10 (8)	.47
Former	60 (67)	41 (56)	.14	61 (50)	.01
Never	24 (27)	31 (42)	.04	51 (42)	.03
Job status[c]					
Nursing	40 (46)	45 (62)	.05	77 (66)	.004
Retired	27 (31)	20 (27)	.62	19 (16)	.01
Nonnursing[d]	20 (23)	8 (11)	.05	20 (17)	.31
Postmenopausal status[e]	78 (93)	60 (85)	.10	96 (81)	.02

Note. BMI = body mass index; BP = blood pressure.
[a]*t*-test comparison of means; χ^2 test comparison of proportions (controls compared with cases).
[b]Not a valid test (cells have expected counts <5).
[c]Only 87 cases, 73 high controls, and 116 low controls had job status information.
[d]Includes homemakers.
[e]Only 84 cases, 71 high controls, and 119 low controls had menopausal status information.

before 1990 (n = 11), premenopausal women (n = 40) or women with missing menopausal status (n = 10), and women using antihypertensive medications (n = 52) did not change these results.

A similar, but nonsignificant, effect estimate was found after restricting analyses to the 66 cases and 133 controls whose blood pressure categorization at recruitment was unchanged by information available from the study evaluation. Job status was not significantly associated with hypertension after adjustment for age. Forcing terms, one at a time, into the models for age,[2] menopausal status, job status, alcohol intake, serum creatinine, hemoglobin, hematocrit, and caffeine intake did not materially change the results. With the ln transformation of patella lead in the final model, the association with hypertension remained significant ($P = .03$). All of these models met the proportional odds assumption of the ordinal models. Although the effect of patella lead on the risk of hypertension in this cohort appeared to be stronger among women whose mean daily alcohol consumption was 14 g/day or more, who were older than 55 years, or who were postmenopausal, these differences were not significant (Table 4).

Hypertension was not associated with either blood lead or tibia lead concentrations in these ordinal regression analyses (Table 3).

Discussion

Results of these analyses indicate a cross-sectional association between bone lead (specifically, patella lead) and the risk of hypertension in middle-aged and elderly women with low blood lead levels. The magnitude of this association within the range of patella lead levels observed was substantial (odds ratio = 1.86 for each 25 μg/g increase in patella lead) and, in the final model, was comparable to a 4 kg/m^2 increase in BMI, a well-established and significant risk factor for hypertension.

By relying on a well-characterized cohort with a relatively homogeneous occupation and a wealth of available prospective dietary, lifestyle, and medical information, these analyses included assessment for numerous potential confounders of the lead–hypertension relationship. However, residual confounding could have influenced our results. Indeed, the apparent association between bone lead and blood pressure could be largely a consequence of unidentified but biologically plausible confounders. For example, alcohol is positively associated with both lead exposure and increases in blood pressure.[15,29] However, alcohol did not play a significant role as a modifier of the lead–hypertension relationship in these analyses (Tables 3 and 4).

Unidentified selection bias may have influenced the results, particularly among individuals knowledgeable about health issues. Although eligible participants were similar to nonparticipants (Table 1), there was differential participation by cases with lower alcohol consumption and controls with higher alcohol consumption, which, because alcohol consumption is a risk factor for greater blood lead concentrations,[29] could bias the results to the null. Otherwise, participating cases and controls differed from nonparticipating cases and controls only insofar as they had slightly higher dietary calcium intakes and were more likely to have a family history of hypertension. There was no evidence of differential participation by other risk factors for hypertension or lead exposure (Table 1). Furthermore, because bone lead concentrations were unknown to eligible participants, and predictors of bone lead in non–occupationally exposed women have not been established, it is very improbable that knowledge of bone lead concentrations could have influenced participation and resulted in unidentified selection bias.

Blood or tibia lead was not associated with hypertension in these analyses. The association of patella lead with hypertension remained borderline significant ($P = .02$) after adjustment for analyses of multiple lead exposure measures. Specifically, with the Bonferroni multiple comparisons procedure, a significance level of 5% corresponds to $P = .02$ for each of the 3 lead measures.[30] Although the statistical significance we found for 1 of 3 lead exposure measures may be due to chance rather than toxicological relevance, the results of a recent study[7] that demonstrated an association of bone lead, but not blood lead, with hypertension in men with low-level lead exposures (mean blood, tibia, and patella lead concentrations of 0.30 μmol/L [6 μg/dL], 21.6 μg/g, and 32.1 μg/g, respectively) argue against this interpretation.

Blood lead levels in our study participants were much lower than those in previous population-based studies of lead and blood pressure.[6,17] For example, among

TABLE 3—Ordinal Regression Models of the Risk of Hypertension as a Function of Blood Lead, Tibia Lead, and Patella Lead and Other Risk Factors[a]

	Model A		Model B		Model C		Model D	
	β ± SE	*P*	β ± SE	*P*	β ± SE	*P*	β ± SE	*P*
Age, y	0.048 ± 0.017	.004	0.046 ± 0.017	.007	0.047 ± 0.017	.006	0.042 ± 0.017	.013
BMI, kg/m^2	0.141 ± 0.050	.005	0.144 ± 0.051	.004	0.142 ± 0.050	.005	0.142 ± 0.051	.005
Diet Ca^{++}, mg/day	0.0001 ± 0.0004	.82	0.0001 ± 0.0004	.75	0.0001 ± 0.0004	.82	0.0001 ± 0.0004	.88
Alcohol, g/day	−0.012 ± 0.012	.30	−0.014 ± 0.012	.26	−0.012 ± 0.012	.30	−0.014 ± 0.012	.25
Diet Na^+, mg/day	−0.001 ± 0.0003	.009	−0.001 ± 0.0003	.008	−0.001 ± 0.0003	.008	−0.001 ± 0.0003	.01
Ever smoke	0.416 ± 0.243	.09	0.414 ± 0.246	.09	0.416 ± 0.244	.09	0.386 ± 0.245	.12
Family hypertension	0.792 ± 0.237	.001	0.805 ± 0.239	.001	0.794 ± 0.237	.001	0.843 ± 0.239	.0004
Blood lead, μmol/L			0.972 ± 1.055	.36				
Tibia lead, μg/g					0.003 ± 0.013	.85		
Patella lead, μg/g							0.025 ± 0.011	.03

Note. SE = standard error; BMI = body mass index.
[a]n = 89 cases of hypertension, 195 normotensive controls.

TABLE 4—Ordinal Regression Models of the Risk of Hypertension as a Function of Patella Lead Concentration in the Final Model and Stratified by Alcohol Intake, Age, and Menopausal Status

	Patella Lead Effect Estimate[a]		
	β ± SE	Odds Ratio Estimate (95% CI)	Interaction *P*[b]
Final model[c]	0.025 ± 0.011	1.03 (1.00, 1.05)*	
Alcohol >14.0 g/day			
Yes (n = 57)	0.073 ± 0.032	1.08 (1.01, 1.14)	.10
No (n = 227)	0.018 ± 0.012	1.02 (1.00, 1.04)	
Age >55 years			
Yes (n = 194)	0.037 ± 0.014	1.04 (1.01, 1.07)	.20
No (n = 90)	0.007 ± 0.019	1.01 (0.97, 1.04)	
Postmenopausal			
Yes (n = 234)	0.035 ± 0.012	1.04 (1.01, 1.06)	.11
No (n = 40)	−0.024 ± 0.035	0.98 (0.91, 1.04)	

Note. SE = standard error; CI = confidence interval.
[a]Parameter estimates for patella lead have been adjusted for age, body mass index (BMI), dietary Na^+, and family history of hypertension. Patella lead concentrations are in μg/g.
[b]Test for interaction between 2 categories and patella lead concentration.
[c]Risk of hypertension as a function of patella lead, age, BMI, dietary Na^+, and family history of hypertension.
*P = .02.

women who participated in the Second National Health and Nutrition Examination Survey and in whom an association of blood lead with blood pressure has been observed, the mean blood lead concentrations ranged from approximately 10 to 13 μg/dL.[6,17] The greater measurement error at lower blood lead levels combined with the limited range of blood lead levels (90% of the values were ≤ 0.29 μmol/L [≤ 6 μg/dL]) may explain the lack of association of blood lead with hypertension in our population. Lastly, evidence that the more bioavailable fraction of blood lead correlates better with bone than with whole blood lead supports the biological plausibility of bone lead as a better determinant of hypertension risk than whole blood lead.[21]

The apparent association of patella but not tibia lead with hypertension in these analyses is as likely to be a random difference as a biologically plausible one, particularly in light of findings from a similar study in men.[7] Tibia lead was significantly associated with hypertension in the men,[7] whereas patella lead was significantly associated with hypertension in our study of women. More mobilizable lead in trabecular bone (patella) may have a greater effect on lead-related changes in blood pressure than lead sequestered in cortical bone (tibia), particularly in a population of women at risk for increased bone resorptive activity. Indeed, the association of patella lead with hypertension was stronger among postmenopausal than premenopausal women (Table 4). Despite the difference in bone site, the magnitude of bone lead's effect on hypertension in the men (a 25 μg/g increase in tibia lead was associated with a 1.6 increased odds of hypertension) was similar to our estimate in women.

In summary, these results support our hypothesized association of low-level lead exposure, as reflected by patella (but not tibia or blood) lead levels, with the risk of hypertension in women. This association was robust to adjustment for confounders and effect modifiers (alcohol and age) identified in previous studies. By using a biomarker of lead exposure that has not been used in previous studies of this topic in women, we demonstrated the sensitivity of this exposure assessment method. We hypothesize that the null or diminished lead–blood pressure association found in previous studies of women may, in part, be a consequence of limitations inherent in the use of blood lead as an exposure index for chronic disease risk, particularly among middle-aged and elderly women with low-level lead exposures. The comparability of our effect estimate with that in a community-based sample of middle-aged and elderly men suggests that a major gender difference in the association between lead and blood pressure is unlikely. Although these results must be confirmed in other populations and in prospective studies to show a causal relationship, these findings suggest that minimizing women's lead exposure throughout adulthood may prove to be an important public health measure for hypertension prevention. □

Contributors

S. A. Korrick planned and designed the study, supervised its execution, analyzed the data, and wrote the paper. D. J. Hunter and H. Hu assisted with the study's design and execution and with data analysis. A. Rotnitzky supervised data analysis. D. J. Hunter, A. Rotnitzky, H. Hu, and F. E. Speizer contributed to the writing of the paper. All 5 authors are guarantors for the integrity of the research.

Acknowledgments

This research was supported by grants ES05257, ES05947, ES00002, RR02635, and CA40356 from the National Institutes of Health (NIH), with funding for ES05947 provided by the US Environmental Protection Agency (EPA). Subjects were evaluated in the outpatient facility of the Brigham and Women's Hospital General Clinical Research Center with support from NIH grant RR02635. The K-XRF instrument used in this work was developed by ABIOMED Inc. (Danvers, Mass) with support from NIH grant ES03918.

We thank Marisa Barr, Laura Hennessy, Rhonda Appelbaum, and Philomena Asante for research assistance. We gratefully acknowledge Kathleen McGaffigan, Karen Corsano, and Mark Shneyder for database management and analytic programming for the study.

References

1. Fiebach NH, Hebert PR, Stampfer MJ, et al. A prospective study of high blood pressure and cardiovascular disease in women. *Am J Epidemiol.* 1989;130:646–654.
2. Frohlich E. Mechanisms contributing to high blood pressure. *Ann Intern Med.* 1983;98(suppl part 2):709–714.
3. Khalil-Manesh F, Gonick HC, Weiler EW, et al. Effect of chelation treatment with dimercaptosuccinic acid (DMSA) on lead-related blood pressure changes. *Environ Res.* 1994;65:86–99.
4. Victery W, Vander AJ, Shulak JM, Schoeps P, Julius S. Lead, hypertension and the renin-angiotensin system in rats. *J Lab Clin Med.* 1982;99:354–362.
5. Revis NW, Zinsmeister AR, Bull R. Atherosclerosis and hypertension induction by lead and cadmium ions: an effect prevented by calcium ion. *Proc Natl Acad Sci U S A.* 1981;78:6494–6498.
6. Harlan WR. The relationship of blood lead levels to blood pressure in the U.S. population. *Environ Health Perspect.* 1988;78:9–13.
7. Hu H, Aro A, Payton M, et al. The relation of bone and blood lead to hypertension. *JAMA.* 1996;275:1171–1176.
8. Weiss ST, Munoz A, Stein A, Sparrow D, Speizer FE. The relationship of blood lead to blood pressure in a longitudinal study of working men. *Am J Epidemiol.* 1986;123:800–808.
9. Pocock SJ, Shaper AG, Ashby D, Delves HT, Clayton BE. The relationship between blood lead, blood pressure, stroke and heart attacks in middle-aged British men. *Environ Health Perspect.* 1988;78:23–30.
10. Kromhout D. Blood lead and coronary heart disease risk among elderly men in Zutphen, the Netherlands. *Environ Health Perspect.* 1988;78:43–46.
11. Hertz-Picciotto I, Croft J. Review of the relation between blood lead and blood pressure. *Epidemiol Rev.* 1993;15:352–373.
12. Harlan WR, Landis JR, Schmouder RL, Goldstein NG, Harlan LC. Blood lead and blood pressure: relationship in the adolescent and adult US population. *JAMA.* 1985;253:530–534.
13. Hense HW, Filipiak B, Keil U. Alcohol consumption as a modifier of the relation between blood lead and blood pressure. *Epidemiology.* 1994;5:120–123.
14. Menditto A, Morisi G, Spagnolo A, Menotti A, the NFR Study Group. Association of blood lead to blood pressure in men aged 55 to 75 years: effect of selected social and biochemical confounders. *Environ Health Perspect.* 1994;102(suppl 9):107–111.
15. Grandjean P, Hollnagel H, Hedegaard L, Christensen JM, Larsen S. Blood lead-blood pressure relations: alcohol intake and hemoglobin as confounders. *Am J Epidemiol.* 1989;129:732–739.
16. Gartside PS. The relationship of blood lead levels and blood pressure in NHANES II: additional calculations. *Environ Health Perspect.* 1988;78:31–34.
17. Schwartz J. Lead, blood pressure, and cardiovascular disease in men and women. *Environ Health Perspect.* 1991;91:71–75.
18. Sharp DS, Becker CE, Smith AH. Chronic low-level lead exposure: its role in the pathogenesis of hypertension. *Med Toxicol.* 1987;2:210–232.
19. Somervaille LJ, Chettle DR, Scott MC, et al. *In vivo* tibia lead measurements as an index of cumulative exposure in occupationally exposed subjects. *Br J Ind Med.* 1988;45:174–181.
20. Landrigan PJ, Todd AC. Direct measurement of lead in bone: a promising biomarker. *JAMA.* 1994;271:239–240.
21. Cake KM, Bowins RJ, Vaillancourt C, et al. Partition of circulating lead between serum and red cells is different for internal and external sources of lead. *Am J Ind Med.* 1996;29:440–445.
22. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol.* 1986;123:894–900.
23. Hypertension Prevention Trial, The. Three-year effects of dietary changes on blood pressure. Hypertension Prevention Trial Research Group. *Arch Intern Med.* 1990;150:153–162.
24. Burger D, Morsillo P, Adams B, Hu H, Milder FL. Automated instrument for making K-X-ray fluorescence measurements in human bone. *Basic Life Sci.* 1990;55:287–293.
25. Hu H, Milder F, Burger DE. X-ray fluorescence measurements of lead burden in subjects with low-level community lead exposures. *Arch Environ Health.* 1990;45:335–341.
26. Armstrong BG, Sloan M. Ordinal regression models for epidemiologic data. *Am J Epidemiol.* 1989;129:191–203.
27. Rothman KJ. *Modern Epidemiology.* Boston, Mass: Little, Brown and Co; 1986:237–283.
28. Schwartz J. Lead, blood pressure, and cardiovascular disease in men. *Arch Environ Health.* 1995;50:31–37.
29. Grandjean P, Olsen NB, Hollnagel H. Influence of smoking and alcohol consumption on blood lead levels. *Int Arch Occup Environ Health.* 1981;48:391–397.
30. Rosner B. *Fundamentals of Biostatistics.* Belmont, Calif: Duxbury Press; 1995:314–317.