Blood Lead, Blood Pressure, and Hypertension in Perimenopausal and Postmenopausal Women

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Context Lead exposures have been shown to be associated with increased blood pressure and risk of hypertension in older men. In perimenopausal women, skeletal lead stores are an important source of endogenous lead exposure due to increased bone demineralization.

Objective To examine the relationship of blood lead level with blood pressure and hypertension prevalence in a population-based sample of perimenopausal and postmenopausal women in the United States.

Design, Setting, and Participants Cross-sectional sample of 2165 women aged 40 to 59 years, who participated in a household interview and physical examination, from the Third National Health and Nutrition Examination Survey conducted from 1988 to 1994.

Main Outcome Measures Associations of blood lead with blood pressure and hypertension, with age, race and ethnicity, cigarette smoking status, body mass index, alcohol use, and kidney function as covariates.

Results A change in blood lead levels from the lowest (quartile 1: range, 0.5-1.6 μg/dL) to the highest (quartile 4: range, 4.0-31.1 μg/dL) was associated with small statistically significant adjusted changes in systolic and diastolic blood pressures. Women in quartile 4 had increased risks of diastolic (>90 mm Hg) hypertension (adjusted odds ratio [OR], 3.4; 95% confidence interval [CI], 1.3-8.7), as well as moderately increased risks for general hypertension (adjusted OR, 1.4; 95% CI, 0.92-2.0) and systolic (>140 mm Hg) hypertension (adjusted OR, 1.5; 95% CI, 0.72-3.2). This association was strongest in postmenopausal women, in whom adjusted ORs for diastolic hypertension increased with increasing quartile of blood lead level compared with quartile 1 (adjusted OR, 4.6; 95% CI, 1.1-19.2 for quartile 2; adjusted OR, 5.9; 95% CI, 1.5-23.1 for quartile 3; adjusted OR, 8.1; 95% CI, 2.6-24.7 for quartile 4).

Conclusions At levels well below the current US occupational exposure limit guidelines (40 μg/dL), blood lead level is positively associated with both systolic and diastolic blood pressure and risks of both systolic and diastolic hypertension among women aged 40 to 59 years. The relationship between blood lead level and systolic and diastolic hypertension is most pronounced in postmenopausal women. These results provide support for continued efforts to reduce lead levels in the general population, especially women.

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SINCE THE 1970S, CONSIDERABLE attention has been paid to the possibility that low levels of lead exposure among adults in the general population can elevate blood pressure and increase the risk for hypertension, a leading risk factor for cardiovascular disease morbidity and mortality.[1-3] Evidence for this association from the epidemiological literature is compelling,[4] but the exact causal nature of the relationship remains controversial.

The notion that lead exposure may influence blood pressure in humans is biologically plausible. Lead induces hypertension in rats,[5,6] and other animal data suggest that lead acts at multiple sites within the cardiovascular system, including direct effects on the excitability and contractility of the heart, alteration of the compliance of the vascular smooth muscle tissue, and direct action on parts of the central nervous system responsible for blood pressure regulation.[2] Evidence in animals also suggests that lead may affect blood pressure through the renin-angiotensin system.[6] Lead is nephrotoxic to humans, and alteration of

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kidney function may precede the development of hypertension.[7,8] However, whether lead affects blood pressure through altering kidney function in humans is not known.

A case-control investigation of men from the Normative Aging Study[9] reported significantly higher levels of lead in skeletal and blood compartments among men with hypertension compared with normotensives. The all-male study population had mean baseline blood lead levels of 6.3 µg/dL, similar to men in the general population.[10] An increase from the midpoint of the lowest quintile to the highest quintile of bone lead was associated with an adjusted odds ratio (OR) of 1.5 (95% confidence interval [CI], 1.1-1.8) for hypertension, suggesting that cumulative lead exposure, represented by bone lead stores, may be an independent risk factor for hypertension in the general population.[9]

Evidence suggests that bone lead stores contribute to circulating levels of lead in blood.[11-13] In particular, blood lead levels in women appear to increase during the menopausal transition, because of the mobilization of skeletal lead stores associated with bone demineralization.[14-18] The impact of these small but significant increases in blood lead in postmenopausal compared with premenopausal women is difficult to interpret, because relatively few studies have examined the health impacts of lead in women. A case-control study[7] of 297 women with hypertension who participated in the Nurses' Health Study showed that increases in bone patella lead levels from the 10th to the 90th percentile were associated with increased risks of hypertension (OR, 1.86, 95% CI, 1.09-3.19). However, information about menopausal status was extremely limited in this study.[7]

The objective of our investigation was to examine the relationship of blood lead levels with blood pressure and hypertension in a population-based sample of perimenopausal and postmenopausal women in the United States. We selected blood pressure and hypertension as outcomes because of the epidemiological data associating relatively low levels of lead in the blood with cardiovascular outcomes[1,2,4,19-38] and because hypertension is a significant health concern for women after menopause.[39]

METHODS

The study population included women from the Third National Health and Nutrition Examination Survey (NHANES III), a cross-sectional sample obtained through a complex survey design, representing the US civilian, noninstitutionalized population. During a 6-year period (1988-1994), participants took part in a household interview and an in-depth physical examination with laboratory tests. Full details of the survey design have been published by the National Center for Health Statistics of the Centers for Disease Control and Prevention.[40]

Our investigation focused on the subset of 2574 women aged 40 to 59 years who participated in the NHANES III survey interview. From this group, 409 women were excluded for the following reasons: 211 did not undergo a physical examination or blood testing; 77 did not have information about blood lead levels; and 121 women of ethnicity other than non-Hispanic black, non-Hispanic white, and Mexican American were excluded because of small numbers in any single self-reported category. The remaining 2165 women constituted the sample used.

Definitions

Blood Pressure and Hypertension. We used the mean of 3 systolic and diastolic blood pressure measurements, all of which were taken by a physician at the end of the 4-hour physical examination that occurred in the NHANES mobile examination center. Women were categorized as hypertensive if any of the following criteria were met: current user of blood pressure medication (self-report), a systolic blood pressure of 140 mm Hg or higher, or a diastolic blood pressure of 90 mm Hg or higher. We also examined separate dichotomous variables for systolic hypertension and diastolic hypertension using these cutoff values, excluding persons who reported being treated for hypertension. More details on measurement of and outcomes related to blood pressure and hypertension in NHANES III have been published elsewhere.[3]

Blood Lead. Blood samples were obtained by venipuncture during the physical examination. Blood lead concentration was measured by graphite furnace atomic absorption spectrophotometry at the laboratories of the National Center for Environmental Health at the Centers for Disease Control and Prevention in Atlanta, Georgia. The assay detection limit was 1.0 µg/dL. Each sample analysis was performed in duplicate, and the mean of both measurements was used in these analyses. All blood lead levels less than 1.0 µg/dL were assigned a value of 0.5 µg/dL to be consistent with previous analyses of NHANES III lead data by other investigators.[10]

Menopausal Status. Women were categorized as premenopausal (ovarian function intact), surgically menopausal (both ovaries removed surgically before cessation of menses), and naturally menopausal (nonsurgical cessation of ovarian function). Women without histories of reproductive surgery were classified as premenopausal if they reported a menstrual period during the previous 12 months and postmenopausal if they did not. Women reporting having undergone hysterectomy (without ovariectomy) within a month of the last menstrual period were assigned a menopausal classification based on their age ($<$51 years, premenopausal; $\geq$51 years, naturally menopausal). Women who underwent bilateral ovariectomy within 1 month of the date of the last menstrual period were classified as surgically menopausal. Women who underwent hysterectomy or ovariectomy more than 1 month after the reported date of the last menstrual period were classified as naturally menopausal. A total of 101 women could not be assigned a menopausal status due to missing information.

Kidney Function. Serum creatinine was measured because it is the most

specific of the 3 measures of kidney function available in NHANES III (serum creatinine, urinary creatinine clearance, and blood urea nitrogen) and was consistent with other recent studies of the effects of lead on the kidney.[41]

Covariates. Information about race and ethnicity (non-Hispanic black, non-Hispanic white, and Mexican American), age (years), cigarette smoking history (current, former, or never), family income, and education was obtained from the household interview. Information about body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) and alcohol use (amount consumed per week) was obtained from the physical examination and examination-associated questionnaire, respectively. A 4-level categorical variable for weekly alcohol intake was created with the following levels: none, less than 1, 1 to 2, or 3 or more drinks per week. The poverty income ratio, a ratio of family income to the poverty level income for a given family size adjusted to the poverty threshold for the year of the interview, was used to create a 3-level family income variable. A participant was assigned a family income higher than the poverty level if the poverty income ratio was more than 1, at or lower than poverty if the poverty income ratio was less than or equal to 1, and missing if the survey participant did not report a family income level. A 4-level education variable was created on the basis of the number of years of education reported by the survey participant (0-11 years = < high school; 12 years = completed high school; 12-15 years = some college; and ≥16 years = completion of college or higher).

Statistical Methods

We used multiple linear regression models to examine the associations of blood lead and menopausal status with systolic and diastolic blood pressures. Analyses that examined systolic and diastolic blood pressure as continuous outcome variables excluded the 368 women with hypertension who were treated. We used multiple logistic regression to examine the risks of hypertension (general, systolic, and diastolic) by categorizing blood lead in terms of quartiles and comparing those women in blood lead quartiles 2, 3, and 4 with those in quartile 1; these analyses were stratified by menopausal status.

Models were constructed based on outcomes known to be biologically associated with blood pressure (age, race and ethnicity, BMI, and serum creatinine), including the study variable blood lead. Potential confounding variables (education, poverty income ratio, alcohol use, and cigarette smoking status) were included if they were found to be significantly associated with blood pressure outcomes in any 1 of the models before the inclusion of blood lead. Final regression covariates included age, race and ethnicity, alcohol use, cigarette smoking status, BMI, and kidney function.

Statistical analyses were conducted using SAS version 6 (SAS Institute, Cary, NC), incorporating the examination sampling weights of NHANES III.[40] The statistical software package SUDAAN version 7.0 (Research Triange Institute, Research Triangle Park, NC) was used to calculate SEs for the estimates, accounting for both the weights and the complex survey design. Linear regression coefficients reported are unstandardized. The significance of regression coefficients was evaluated using the Wald χ^2 test. Statistical tests for trends of categorical variables were carried out in regression models by coding levels as integers (scores) and evaluating tests for significance on the slope of the regression line. Statistical tests with $P \leq .05$ were considered statistically significant. All estimates of proportions, regression coefficients, and ORs are weighted to the 1990 US Census population.

RESULTS

Overall, the mean blood lead level for women aged 40 to 59 years was 2.9 µg/dL, and the means for the quartiles of blood lead ranged from 1.0 µg/dL to 6.3 µg/dL in the lowest and highest quartile, respectively (TABLE 1). Women in the higher quartiles of blood lead tended to be older, current smokers, regular drinkers, poorer, less educated, and more likely to be non-Hispanic black than those in the lower quartiles. All of these variables were significantly associated with blood lead level.

Of the 2165 women in the sample, 604 were classified as hypertensive based on their systolic and diastolic blood pressures (n = 231, untreated), as well as whether they self-reported currently taking antihypertensive medications (n = 373). Of those that were untreated (n = 231), 123 had systolic hypertension only, 30 had diastolic hypertension only, and 78 had both systolic and diastolic hypertension. Of those who were treated for hypertension (n = 373), 202 had neither systolic nor diastolic hypertension, 102 had systolic hypertension only, 14 had diastolic hypertension only, 50 had both systolic and diastolic hypertension, and 5 did not have a systolic or diastolic blood pressure measurement during the examination.

In these crude analyses, blood lead quartile was significantly associated with systolic blood pressure ($P = .03$) but not diastolic blood pressure ($P = .86$) (TABLE 2). A significant dose-response existed between blood lead quartile and general hypertension prevalence, with 19.4% of women having general hypertension in the lowest quartile compared with 28.3% in the highest quartile. However, although dose-response trends appeared to exist, blood lead quartile was not significantly associated specifically with systolic or diastolic hypertension prevalence ($P = .09$ and $P = .25$, respectively).

Systolic and Diastolic Blood Pressure

In multivariate analyses, blood lead was significantly associated with both systolic and diastolic blood pressures (TABLE 3). In these regression models, a difference in blood lead levels between the lowest and highest quartiles was associated with a difference of 1.7 mm Hg in systolic blood pressure and

1.4 mm Hg in diastolic blood pressure, after adjustment for age, race and ethnicity, cigarette smoking, BMI, alcohol use, and kidney function. Omission of the serum creatinine variable in the multivariable models for blood lead and blood pressure (both systolic and diastolic) did not alter the significance of the blood lead variable.

General Hypertension

Before incorporating blood lead level in the multiple logistic regression model (TABLE 4), the most important factors independently increasing the ORs of general hypertension in women included increasing age, being non-Hispanic black, having an alcohol intake of less than 1 drink per week, and increasing BMI. Adding blood lead level to the model did not greatly alter any of

Table 1. Weighted Descriptive Characteristics of Adult Women Aged 40 to 59 Years Participating in the Third National Health and Nutrition Examination Survey*

Characteristic	Total (N = 2165)	Blood Lead Quartile				*P* Value
		Quartile 1 (n = 568)	Quartile 2 (n = 498)	Quartile 3 (n = 556)	Quartile 4 (n = 543)	
Blood lead level, mean (range), µg/dL	2.9 (0.50-31.1)	1.0 (0.5-1.6)	2.1 (1.7-2.5)	3.2 (2.6-3.9)	6.4 (4.0-31.1)	
Race and ethnicity, %						
Non-Hispanic white	83.9	87.4	86.5	83.4	76.3	<.001
Non-Hispanic black	11.7	8.1	9.3	12.6	18.5	
Mexican American	4.4	4.5	4.2	4.1	5.2	
Age, mean (SE), y	48.2 (0.2)	46 (0.32)	48 (0.44)	49 (0.34)	50.4 (0.39)	<.001
Body mass index, mean (SE)	27.6 (0.25)	28.4 (0.58)	27.5 (0.31)	27.6 (0.34)	26.9 (0.29)	.04
Cigarette smoking history, %						
Current	25.0	8.1	20.2	35.2	42.8	<.001
Former	25.5	30.4	25.2	19.2	26.5	
Never	49.5	61.5	54.6	45.6	30.7	
Alcohol use, %						
None	56.8	62.6	60.1	54.0	47.8	<.001
<1 per week	15.2	14.5	15.9	15.6	14.6	
1-2 per week	17.1	14.5	14.4	21.4	18.6	
≥3 per week	11.0	8.5	9.5	9.0	19.0	
Household income, %						
At or below poverty	8.8	6.1	7.7	8.0	15.1	<.001
Above poverty	84.9	90.3	84.4	84.8	78.0	
Missing	6.3	3.6	8.0	7.2	6.9	
Education, %						
<High school	18.9	13.0	16.7	22.6	25.6	<.001
Completed high school	40.0	40.0	43.1	38.2	38.5	
Some college	19.9	18.4	21.9	21.0	18.5	
College or higher	21.1	28.6	18.3	18.2	17.5	

*Body mass index is calculated as weight in kilograms divided by the square of height in meters. *P* values obtained from χ^2 test (categorical variables) or analysis of variance (continuous variables) based on an overall test across quartiles.

Table 2. Weighted Distributions of Blood Pressure–Related Variables Among Adult Women Aged 40 to 59 Years Participating in the Third National Health and Nutrition Examination Survey

Characteristic	Total (N = 2165)	Blood Lead Quartile				*P* Value*	*P* for Trend
		Quartile 1 (n = 568)	Quartile 2 (n = 498)	Quartile 3 (n = 556)	Quartile 4 (n = 543)		
Blood lead level, mean (range), µg/dL	2.9 (0.50-31.1)	1.0 (0.5-1.6)	2.1 (1.7-2.5)	3.2 (2.6-3.9)	6.4 (4.0-31.1)		
Blood pressure, mean (SE), mm Hg							
Systolic	118.7 (0.48)	117.2 (0.95)	117.7 (0.83)	119.3 (1.10)	121.2 (0.92)	.03	<.001
Diastolic	74.1 (0.29)	73.7 (0.51)	74.2 (0.53)	74.2 (0.62)	74.3 (0.62)	.86	.79
Hypertension, %							
General†	23.0	19.4	20.6	25.5	28.3	.05	<.001
Systolic >140 mm Hg‡	8.4	6.2	6.6	10.4	11.4	.09	<.001
Diastolic >90 mm Hg‡	4.7	3.1	4.1	5.1	7.1	.25	<.001

**P* values obtained from χ^2 test (categorical variables) or analysis of variance (continuous variables) based on an overall test across quartiles.
†General hypertension defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or self-report of prescription antihypertensive treatment.
‡Excludes women who reported being currently treated for hypertension.

the existing associations between age, race and ethnicity, alcohol intake, and BMI. For women in the highest 2 quartiles of blood lead level relative to the lowest quartile, the adjusted ORs of hypertension were elevated but not significantly (OR, 1.3; 95% CI, 0.90-2.0 and OR, 1.4; 95% CI, 0.90-2.0, for quartiles 3 and 4, respectively). Separate models of these associations for premenopausal women and postmenopausal women yielded similar results, with the exception that serum creatinine was strongly associated with general hypertension in premenopausal women.

Systolic and Diastolic Hypertension

After similar adjustment, a weak association existed for untreated systolic hypertension. For women in the fourth quartile of blood lead, the ORs were the highest (OR, 1.55; 95% CI, 0.72-3.20) (TABLE 5). The adjusted ORs of diastolic hypertension relative to women in the lowest quartile of blood lead level increased with a clear dose-response (quartile 2: OR, 1.5; 95% CI, 0.61-3.7; quartile 3: OR, 2.1; 95% CI, 0.76-5.9; and quartile 4: OR, 3.4; 95% CI, 1.3-8.7).

Stratification by menopausal status revealed a weak dose-response relationship between blood lead level and systolic hypertension in premenopausal women, and a significantly elevated OR of systolic hypertension in postmenopausal women in the second and third quartiles of blood lead relative to women in the lowest quartile (quartile 2: OR, 3.0; 95% CI, 1.3-6.9 and quartile 3: OR, 2.7;

Table 3. Unstandardized Regression Coefficients for Blood Lead and Systolic Blood Pressure and Diastolic Blood Pressure in Women Aged 40 to 59 Years Not Treated for Hypertension*

	All Women (N = 1786)	*P* Value	Premenopausal Women (n = 1084)	*P* Value	Postmenopausal Women (n = 633)	*P* Value
Systolic Blood Pressure, Regression Coefficients (SE)						
R^2	0.22		0.22		0.19	
Intercept	61.1 (3.88)		57.4 (6.62)		56.1 (7.22)	
Blood lead, μg/dL	0.32 (0.16)	.03	0.14 (0.26)	.59	0.42 (0.21)	.29
Age, y	0.70 (0.08)	<.001	0.77 (0.15)	<.001	.86 (0.14)	.26
Race and ethnicity						
Non-Hispanic black	−4.01 (1.07)	<.001	−4.82 (1.4)	.002	−3.89 (2.04)	.32
Mexican American	−1.25 (0.97)		−1.54 (1.31)		−1.01 (1.61)	
Non-Hispanic white	1.0		1.0		1.0	
Alcohol use						
≥3 per week	−2.10 (1.55)	.32	−1.78 (2.12)	.77	−2.31 (3.26)	.30
1-2 per week	−1.11 (1.39)		0.60 (1.37)		−5.33 (2.78)	
<1 per week	0.18 (1.12)		0.14 (1.29)		0.86 (2.33)	
None	1.0		1.0		1.0	
Cigarette smoking status						
Current	1.24 (1.09)	.32	0.77 (1.27)	.83	0.72 (1.81)	.20
Former	0.80 (1.43)		0.22 (1.89)		1.03 (1.43)	
Never	1.0		1.0		1.0	
Body mass index	0.81 (0.08)	<.001	0.82 (0.10)	<.001	0.79 (0.17)	<.001
Serum creatinine	1.10 (1.53)	.002	2.64 (0.96)	.006	−2.96 (2.50)	.01
Diastolic Blood Pressure, Regression Coefficients (SE)						
R^2	0.14		0.17		0.12	
Intercept	56.8 (2.49)		52.2 (4.52)		61.5 (3.91)	
Blood lead, μg/dL	0.25 (0.09)	.009	0.38 (0.25)	.12	0.14 (0.13)	.04
Age, y	0.07 (0.05)	.13	0.13 (0.11)	.25	0.07 (0.06)	<.001
Race and ethnicity						
Non-Hispanic black	−1.51 (0.50)	.001	−1.93 (0.71)	.002	−1.18 (0.89)	.16
Mexican American	0.65 (0.58)		0.92 (0.79)		0.47 (1.10)	
Non-Hispanic white	1.0		1.0		1.0	
Alcohol use						
≥3 per week	−2.04 (0.94)	.18	−2.31 (1.62)	.54	−1.39 (1.33)	.07
1-2 per week	−0.73 (0.77)		−0 (0.82)		−2.57 (1.43)	
<1 per week	−0.14 (0.73)		0.09 (0.97)		−0.30 (1.18)	
None	1.0		1.0		1.0	
Cigarette smoking status						
Current	2.83 (0.70)	<.001	3.25 (0.94)	.002	2.18 (1.21)	.76
Former	1.16 (0.90)		1.39 (1.21)		0.09 (0.78)	
Never	1.0		1.0		1.0	
Body mass index	0.47 (0.05)	<.001	0.51 (0.05)	<.001	0.39 (0.10)	<.001
Serum creatinine	1.11 (1.02)	.28	2.26 (0.58)	<.001	−2.15 (0.87)	.24

*Body mass index is calculated as weight in kilograms divided by the square of height in meters. A total of 69 women could not be assigned a menopausal status due to missing data.

95% CI, 1.2-6.2). A dose-response relationship was apparent for blood lead quartile and diastolic hypertension, which was particularly striking for postmenopausal women.

COMMENT

To our knowledge, this is the first study to examine the effects of blood lead and blood pressure in perimenopausal women. After accounting for age, race and ethnicity, alcohol intake, cigarette smoking status, BMI, and kidney function, we found a significant association between blood lead and systolic and diastolic hypertension prevalence among women aged 40 to 59 years in the US population. We selected this population to analyze the role of menopausal status, which we and others have shown can influence blood lead levels in women.[14-17,42,43] Furthermore, this is the age range at which the risks for hypertension increase markedly in women.[39,44] The highest quartile of blood lead (mean, 6.3 µg/dL) was associated with a 3.4-fold increase in the risks of diastolic hypertension (95% CI, 1.3-8.7) relative to those in the lowest blood lead quartile (mean, 1.0 µg/dL). These risks were considerably higher for postmenopausal women. In addition, blood lead was a significant, positive predictor of both elevated systolic and diastolic blood pressure in these women. A difference in blood lead levels between the lowest quartile and the highest quartile was associated with a difference of 1.7 mm Hg in systolic blood pressure and 1.4 mm Hg in diastolic blood pressure. Blood lead is among the few predictors of both systolic and diastolic blood pressures in perimenopausal US women. Per unit change, blood lead was a stronger predictor of diastolic blood pressure than age.

Table 4. Adjusted Odds Ratio of General Hypertension, Stratified by Menopausal Status*

	Odds Ratio (95% Confidence Interval)			
		Adjusted†		
	All Women (N = 2165)	All Women (N = 2165)	Premenopausal Women (n = 1214)	Postmenopausal Women (n = 850)
Blood lead quartile				
1		1.0	1.0	1.0
2		1.0 (0.63-1.6)	0.78 (0.38-1.6)	0.73 (0.40-1.3)
3		1.3 (0.87-2.0)	1.4 (0.82-2.4)	1.3 (0.75-2.2)
4		1.4 (0.92-2.0)	1.5 (0.78-2.8)	1.3 (0.68-2.3)
Age, y	1.1 (1.1-1.1)	1.1 (1.1-1.1)	1.1 (1.0-1.1)	1.1 (1.0-1.2)
Race and ethnicity				
Non-Hispanic black	2.3 (1.7-3.1)	2.2 (1.7-2.9)	2.4 (1.5-3.7)	2.2 (1.5-3.2)
Mexican American	0.90 (0.60-1.4)	0.90 (0.60-1.3)	1.1 (0.60-1.7)	0.80 (0.40-1.5)
Non-Hispanic white	1.0	1.0	1.0	1.0
Alcohol use				
≥3 per week	1.0 (0.60-1.7)	1.0 (0.60-1.8)	0.90 (0.40-1.9)	1.0 (0.40-2.7)
1-2 per week	0.90 (0.70-1.3)	1.0 (0.70-1.3)	1.2 (0.80-1.6)	0.70 (0.40-1.4)
<1 per week	1.9 (1.2-3.0)	1.9 (1.2-3.1)	1.9 (0.90-4.0)	1.8 (0.90-3.7)
None	1.0	1.0	1.0	1.0
Cigarette smoking status				
Former	0.80 (0.50-1.4)	0.90 (0.50-1.4)	0.80 (0.40-1.5)	0.90 (0.50-1.6)
Current	1.0 (0.70-1.4)	1.1 (0.80-1.6)	1.5 (0.80-2.9)	0.90 (0.50-1.4)
Never	1.0	1.0	1.0	1.0
Body mass index	1.1 (1.1-1.1)	1.1 (1.1-1.2)	1.1 (1.1-1.1)	1.1 (1.1-1.2)
Serum creatinine	2.5 (0.60-10.1)	2.3 (0.60-9.2)	7.4 (1.7-32.7)	1.1 (0.50-2.4)

*Body mass index is calculated as weight in kilograms divided by the square of height in meters. General hypertension defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or self-report of prescription antihypertensive treatment. A total of 101 women could not be assigned a menopausal status due to missing data. For every unit change in each of these variables (age, body mass index, serum creatinine), the regression coefficient represents the increase in odds of hypertension for each covariate.
†Adjusted for age, race, alcohol intake, cigarette smoking status, body mass index, and serum creatinine clearance.

The results are consistent with those of Korrick et al,[7] who found an association between self-reported hypertension and bone lead in older women. In a study of 45-year-old women living in Copenhagen County, Denmark, higher blood lead levels were associated with elevated diastolic blood pressure.[29] Neither study accounted for menopausal status in either blood lead level or hypertension analyses.

In analyses of systolic and diastolic blood pressures, the relationship between blood lead and blood pressure was not stronger for blacks than for whites, nor did blood lead levels explain racial differences in hypertension prevalence. In fact, the blood lead and hypertension relationships reported appeared to be less pronounced among blacks compared with the cohort as a whole. However, stratification of the cohort by race and ethnicity resulted in small sample sizes in each blood lead quartile, limiting precision.

The associations of blood lead with systolic and diastolic hypertension were much more pronounced for postmenopausal women than for premenopausal women. The reasons for this association are unclear. Postmenopausal women may be more sensitive to the hypertensive effects of lead because of loss of estrogen at menopause.[44] Estrogen has been postulated to protect women from age-related increases in blood pressure,[44] although results from a large randomized clinical trial have not supported this hypothesis.[45] This observation also may reflect complex relationships between bone lead and blood lead, which are altered by the changes in bone mineral metabolism that accompany the menopausal transition.

Whether lead affects blood pressure through altering kidney function in humans is not known. Lead is nephrotoxic to humans, and alteration of kidney function may precede the development of hypertension.[7,8] Kidney function, as measured by serum creatinine, was found to be significantly positively associated with both systolic and diastolic blood pressures in premenopausal women who are untreated for

hypertension. Perhaps this reflects that the kidney can be a common pathway for blood pressure regulation, and the effect of lead on the kidney is only part of the relationship between kidney function and blood pressure. However, controlling for kidney function did not reduce the association of blood lead with blood pressure and hypertension, as would be expected if kidney function were along the causal pathway. In the present investigation, serum creatinine was both a sensitive and significant predictor of general hypertension in premenopausal women. For every unit increase in serum creatinine, the risks of hypertension increased more than 7-fold (OR, 7.4; 95% CI, 1.7-32.7). However, a significant association between lead and general hypertension was not found.

The mechanisms of lead-induced hypertension are not well-characterized, even in animal models. One hypothesis is that lead induces hypertension through direct effects on the kidney. A recent retrospective study of 509 healthy participants of the Normative Aging Study found blood lead levels to be significantly positively correlated with serum creatinine levels.[41] A study of lead-exposed workers, with high blood lead levels (mean, 37 µg/dL), reported increases in diastolic blood pressure and in levels of urinary biomarkers for renal function.[7] Batuman et al[46] reported that patients with essential hypertension who had reduced renal function had significantly more chelatable lead than those with essential hypertension with normal renal function.

In the present study, kidney function measured by serum creatinine did not appear to mediate the associations between blood lead and blood pressure. Thus, lead may act on blood pressure through effects on the vasculature or central nervous system, or more sensitive measures of renal function may be required to test mechanistic hypotheses. However, Staessen[47] reported no association between renal markers of lead toxicity and blood pressure in a large cohort study of women. The magnitude of the effects of blood lead on blood

Table 5. Adjusted Odds Ratios for Hypertension, Systolic Hypertension, and Diastolic Hypertension by Blood Lead Quartile*

	Blood Lead Quartile			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
All Premenopausal and Postmenopausal Women				
No. in sample	568	498	556	543
Blood lead, mean (range), µg/dL	1.0 (0.5-1.6)	2.1 (1.7-2.5)	3.2 (2.6-3.9)	6.4 (4.0-31.1)
General hypertension, OR (95% CI)†	1.0	1.0 (0.63-1.6)	1.3 (0.87-2.0)	1.4 (0.92-2.0)
Premenopausal and Postmenopausal Women Untreated for Hypertension				
No. in sample	433	476	438	445
Blood lead, mean (range), µg/dL	0.94 (0.5-1.5)	2.0 (1.6-2.5)	3.1 (2.6-3.8)	6.2 (3.9-31.1)
Systolic hypertension >140 mm Hg, OR (95% CI)‡	1.0	0.89 (0.41-1.9)	1.4 (0.75-2.7)	1.55 (0.72-3.20)
Diastolic hypertension >90 mm Hg, OR (95% CI)‡	1.0	1.5 (0.61-3.7)	2.1 (0.76-5.9)	3.4 (1.3-8.7)
All Premenopausal Women				
No. in sample	304	302	300	308
Blood lead, mean (range), µg/dL	0.8 (0.5-1.4)	1.8 (1.5-2.1)	2.7 (2.2-3.3)	5.4 (3.4-28.7)
General hypertension, OR (95% CI)†	1.0	0.78 (0.38-1.6)	1.4 (0.82-2.4)	1.5 (0.78-2.8)
Premenopausal Women Untreated for Hypertension				
No. in sample	279	277	262	266
Blood lead, mean (range), µg/dL	0.8 (0.5-1.4)	1.8 (1.5-2.1)	2.7 (2.2-3.3)	5.4 (3.4-28.7)
Systolic hypertension >140 mm Hg, OR (95% CI)‡	1.0	0.88 (0.29-2.7)	1.4 (0.49-3.7)	1.6 (0.62-4.2)
Diastolic hypertension >90 mm Hg, OR (95% CI)‡	1.0	1.1 (0.31-3.6)	1.8 (0.76-4.2)	3.5 (0.89-13.4)
All Postmenopausal Women				
No. in sample	206	227	203	214
Blood lead, mean (range), µg/dL	1.3 (0.5-1.9)	2.5 (2.0-3.1)	3.9 (3.2-4.6)	7.4 (4.7-31.1)
General hypertension, OR (95% CI)†	1.0	0.73 (0.40-1.3)	1.3 (0.75-2.2)	1.3 (0.68-2.3)
Postmenopausal Women Untreated for Hypertension				
No. in sample	163	148	166	156
Blood lead, mean (range), µg/dL	1.4 (0.5-2.0)	2.6 (2.1-3.0)	3.8 (3.1-4.6)	7.4 (4.7-31.1)
Systolic hypertension >140 mm Hg, OR (95% CI)‡	1.0	3.0 (1.3-6.9)	2.7 (1.2-6.2)	2.6 (0.89-7.5)
Diastolic hypertension >90 mm Hg, OR (95% CI)‡	1.0	4.6 (1.1-19.2)	5.9 (1.5-23.1)	8.1 (2.6-24.7)

Abbreviations: OR, odds ratio; CI, confidence interval.
*Adjusted for age, race, alcohol intake, cigarette smoking status, body mass index (calculated as weight in kilograms divided by the square of height in meters), and serum creatinine.
†General hypertension defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or self-report of prescription antihypertensive treatment.
‡Excludes women who reported currently receiving antihypertensive treatment.

pressure observed in this study are similar to previous investigations, including 1 study of women.[29]

Several cross-sectional[21-24,29-31,33,48] and prospective[29,31,35] population-based studies on the association of lead with systolic and diastolic blood pressures have been performed from the mid-1980s. The results of these studies have been mixed, but there is considerable concordance with the directionality of the observed associations, with most consistently finding a weak-positive association between blood lead and both systolic and diastolic blood pressure in men, women, blacks, and whites.[4] A meta-analysis by Schwartz[38] of 15 studies of lead and systolic blood pressure in men estimated that a change in blood lead from 5 to 10 µg/dL was associated with an increase of 1.5 mm Hg in systolic blood pressure (95% CI, 0.87-1.63 mm Hg), which compares well with the corresponding estimate from our study (1.6 mm Hg; 95% CI, 0.97-2.20). The adjusted ORs from multiple logistic regression models performed separately for premenopausal and postmenopausal women (Table 5) show a consistent, although not always significant, dose-response relationship between blood lead quartile and risks of hypertension. These subgroup analyses resulted in smaller numbers of women in the models, and this is reflected in the wide CIs in some of the estimates.

The conventional predictors of blood lead in the current US population have been published in a previous NHANES III analysis by Brody et al.[10] Other non-bone density–related exposures that can result in elevated blood lead levels in the United States include residential exposure to lead paint, residential proximity to a lead smeltering facility, occupational exposure (lead smelter, battery manufacturing, welding, or bridge painting), cigarette smoking, and alcohol intake.[15] Those variables associated with lead and also known to be associated with blood pressure and hypertension (ie, potential confounders) were adjusted for in the blood lead and blood pressure and hypertension analyses of our study.

The human skeleton is a dynamic physiological compartment of mineral metabolism. Women lose as much as 50% of trabecular bone and 30% of cortical bone during their lifetime, and 30% to 50% of this bone loss occurs in the early postmenopausal years.[49-53] Estrogen deficiency appears to play a significant role in bone loss.[51,54]

Observational evidence suggests that lead may be mobilized from the skeleton during periods of increased bone demineralization, such as during pregnancy and lactation,[12,55-57] very old age,[58] and menopause.[14-16,59] Two cross-sectional studies[14,15] of US women that were performed using data from the second NHANES (NHANES II, 1976-1980) and the Hispanic HANES (1982-1984) documented that postmenopausal women have significantly higher blood lead levels than premenopausal women, controlling for age and other factors related to exogenous lead exposure. Another study[59] also identified menopausal status as an independent predictor of blood lead levels in a random sample of Scandinavian women.

Hu et al[60] noted that bone lead may be a more appropriate marker of lead exposure for chronic disease outcomes such as hypertension. The present study is a cross-sectional study in that the exposures and the outcomes were measured simultaneously. The relevant exposures affecting blood pressure and hypertension may occur months or years before the observed effect. For example, the average BMI during the 5 years preceding the blood pressure measurement may have more explanatory power than BMI measured on the same day as the blood pressure. Likewise, cumulative lead exposure during the preceding decade, bone lead burden, or serum creatinine may be more predictive of blood pressure than blood lead level measured on the same day as blood pressure. Evidence suggests that bone lead stores can contribute to circulating levels of lead in blood.[11-13]

The findings of our study are inconsistent with the notion of a latency period of months to years between the onset of perimenopausal bone loss resulting in increased endogenous lead exposure, followed by a chronic effect of lead on blood pressure. A study by Cake et al[61] suggests that bone lead released into the blood may be more bioavailable than lead resulting from environmental exposure. Therefore, if blood lead in perimenopausal women is more driven by bone lead levels, it is possible that blood lead levels may be a more sensitive predictor of blood pressure outcomes in this population, because it represents liberated skeletal lead stores.

Important methodological challenges exist in observational studies of lead exposure and blood pressure and hypertension. First, if an association between lead exposure and blood pressure exists, lead is most likely responsible for a relatively small effect on blood pressure, and thus, this association may be difficult to consistently ascertain in different populations. Second, when examining small effects, the issue of residual confounding, beyond that which is controlled in the analysis, becomes extremely important. In such cases, what may be interpreted as a small effect of blood lead on blood pressure may actually be due to inadequate control of confounding factors. However, the restricted age range chosen for this investigation helps to minimize the effect of confounding by age, which is strongly related to blood lead, blood pressure, and hypertension. Third, because the mechanisms by which lead may act on blood pressure in humans are not well understood, investigators may tend to include more covariates than necessary in their models or use mechanical, stepwise approaches to modeling. The true size of the effect may be decreased by overcontrolling. This is a particular problem in studies of environmental lead exposure, because blood lead levels are highly correlated with race and ethnicity, income, and education,[10] which also may be risk factors for outcomes such as hypertension.[49]

Whether bone or blood is the appropriate biomarker for lead exposure in studies of chronic disease outcomes is

uncertain.[60] Blood lead is a marker of relatively recent exposures to lead. Hypertension in adults that may be associated with past exposures to lead is consistent with a follow-up study of lead-poisoned children in whom the risks for hypertension were significantly higher than they were in controls matched by age, sex, race and ethnicity, and neighborhood.[50] Bone lead is a more appropriate marker for chronic exposure; however, its interpretation depends on an understanding of bone physiology and events such as pregnancy and menopause.[11] Future studies of blood pressure and hypertension should consider blood lead and bone lead as independent factors influencing the risk for hypertension.

The R^2 values in Table 3 suggest that the models explain 22% and 14% of the variation in systolic and diastolic blood pressure, respectively. We interpret this to mean that much of the variation in blood pressure is random or due to unknown or immeasurable factors. Because blood pressure has been so well studied, it is unlikely that there are undiscovered factors responsible for the remaining unexplained variation.

Other factors that contribute to the variation in blood lead levels observed in our study include measured and unmeasured aspects of conventional and bone density–related predictors of blood lead, as well as other variables that were not measured by NHANES. However, we controlled for all of the known factors associated with blood pressure and hypertention,[3] including alcohol intake. This approach presumably minimizes residual confounding of our estimate of the associations of blood lead with blood pressure and hypertension.

Vital status data are not yet available on the NHANES III cohort. However, a recent analysis of men and women from the NHANES II cohort by Lustberg and Silbergeld[62] found elevated blood lead levels to be associated with a dose-related increase in deaths due to hypertension-related coronary heart disease and stroke for both men and women. Although the timing of NHANES II resulted in higher blood lead levels than our data in our population, the effects observed in our study also suggest that lead acts on the cardiovascular system and much lower levels in the blood.

From a public health perspective, the most important and troubling implication of these findings is that lead appears to increase blood pressure in women at very small increments above 1.0 µg/dL, well below what is considered deleterious in adults. The mean blood lead level in this sample of women was 2.9 µg/dL. These results demonstrate effects of lead at levels less than the US occupational blood lead exposure limits (40 µg/dL) and even less than the current Centers for Disease Control and Prevention level of concern for preventing lead poisoning in children (10 µg/dL). Finally, the findings from our study of associations of blood lead with systolic and diastolic hypertension and blood pressure among women in the general population lend support for further studies on the health effects of bone lead mobilization during the menopausal transition. These results provide support for continued efforts to reduce lead levels in the general population, especially women.

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Acquisition of data: Nash.
Analysis and interpretation of data: Nash, Magder, Lustberg, Rubin, Kaufmann, Silbergeld.
Drafting of the manuscript: Nash, Sherwin, Rubin, Kaufmann, Silbergeld.
Critical revision of the manuscript for important intellectual content: Nash, Magder, Lustberg, Sherwin, Rubin, Kaufmann, Silbergeld.
Statistical expertise: Magder.
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Study supervision: Nash, Sherwin, Rubin, Kaufmann, Silbergeld.
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