Blood Pressure in Relation to Environmental Lead Exposure in the National Health and Nutrition Examination Survey 2003 to 2010

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Abstract—In view of the declining environmental lead exposure in the United States, we analyzed the National Health and Nutrition Examination Survey (2003–2010) for association of blood pressure and hypertension with blood lead. The 12 725 participants included 21.1% blacks, 20.5% Hispanics, 58.4% whites, and 48.7% women. Blacks compared with non-Blacks had higher systolic and diastolic pressures (126.5 versus 123.9 and 71.9 versus 69.6 mm Hg) and higher hypertension prevalence (44.7 versus 36.8%). Blood lead was lower in whites than in non-whites (1.46 versus 1.57 µg/dL) and in women than in men (1.25 versus 1.80 µg/dL). In multivariable analyses of all participants, blood lead doubling was associated with higher ($P \leq 0.0007$) systolic and diastolic pressure (+0.76 mm Hg; 95% confidence interval, 0.38–1.13 and +0.43 mm Hg; 0.18–0.68), but not with the odds of hypertension (0.95; 0.90–1.01; $P=0.11$). Associations with blood lead were nonsignificant ($P \geq 0.09$) for systolic pressure in women and for diastolic pressure in non-whites. Among men, systolic pressure increased with blood lead ($P \leq 0.060$) with effect sizes associated with blood lead doubling ranging from +0.65 mm Hg in whites to +1.61 mm Hg in blacks. For systolic pressure, interactions of ethnicity and sex with blood lead were all significant ($P \leq 0.019$). In conclusion, small and inconsistent effect sizes in the associations of blood pressure with blood lead likely exclude current environmental lead exposure as a major hypertension cause in the United States. **(*Hypertension*. 2015;65:62-69. DOI: 10.1161/HYPERTENSIONAHA.114.04023.)** ● **Online Data Supplement**

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Voluntary and regulatory restrictions since the 1970s on the use of lead in gasoline, paint, and soldered food cans resulted in a progressive decline in the exposure of populations to lead. In the United States, the National Health and Nutrition Examination Survey (NHANES) documented a progressive decline in the geometric blood lead concentration over time. Among adults, mean blood lead levels decreased from 13.1 µg/dL in NHANES II (1976–1980)[1,2] to 2.76 µg/dL in NHANES III (1988–1994)[3] and next to 1.64 µg/dL in NHANES IV (1999–2002).[3]

High-level lead exposure causes hypertension.[4,5] In a previous meta-analysis, we reported that a 2-fold increase in the blood lead concentration was associated with a higher blood pressure with estimated effect sizes of 1.0 mm Hg (95% confidence interval [CI], 0.5–1.4 mm Hg) systolic and 0.6 mm Hg (0.4–0.8 mm Hg) diastolic.[4] In our analysis of NHANES III data,[6] the median blood lead concentrations among blacks and whites of either sex ranged from 2.1 to 4.2 µg/dL. The multivariable-adjusted changes in blood pressure associated with a doubling of blood lead were inconsistent across the 4 ethnicity-sex strata and ranged from +0.1 mm Hg ($P=0.80$) to +1.2 mm Hg ($P=0.004$) systolic and from −0.6 mm Hg ($P=0.0003$) to +0.5 mm Hg ($P=0.047$) diastolic.[6] In view of the continuing declining environmental lead exposure in the United States,[1,3] and the apparent ethnic diversity in NHANES III in the associations of blood pressure with blood lead,[6,7] we aimed at reanalyzing the relationship between blood pressure and blood lead in NHANES IV (2003–2010).

Methods

Field Work

The US National Center for Health Statistics (Centers for Disease Control and Prevention, Atlanta, GA) conducted NHANES IV (1999–2012). Interviews were conducted at the participants' homes. The comprehensive physical examinations, which included measurements of anthropometric characteristics, blood pressure, and collection of blood and urine samples, took place at mobile examination

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centers. The National Center for Health Statistics Institutional Review Board approved the interviews, physical examinations, and the procedure to obtain written informed consent. The details of the field work are described in the Expanded Methods in the online-only Data Supplement (page S2).

Selection of Participants

The NHANES IV data considered for the current analysis were collected in 7 stages: 1999 to 2000, 2001 to 2002, 2003 to 2004, 2005 to 2006, 2007 to 2008, 2009 to 2010, and 2011 to 2012. The pooled data initially comprised 71916 people examined from 1999 until 2012. In keeping with our previous report,[6] we planned to account for dietary habits. This forced us to excluded participants examined from 1999 to 2002, because the protocol for collecting dietary information substantially changed in 2002 and people examined in 2011 and 2012, because dietary information was lacking in the online database (accessed February 20, 2014). After exclusion of participants with missing or unreliable data, the number of analyzed participants totaled 12725. The Expanded Methods in the online-only Data Supplement (pages S2–S3) provide detailed information on selection and exclusion criteria and on the representativeness of the participants retained in the analysis. Self-reported ethnicity was categorized as non-Hispanic white, non-Hispanic black, and Hispanic.

Measurements

At mobile examination centers, trained observers measured anthropometric characteristics and blood pressure. Blood pressure was the average of ≤3 readings. The number of blood pressure readings available for analysis was 3 in 11601 participants (91.2%), 2 in 626 (4.9%), and only 1 in 498 (3.9%). Hypertension was a blood pressure of ≥140 mm Hg systolic or 90 mm Hg diastolic or the use of antihypertensive drugs. Pulse pressure was the difference of systolic minus diastolic blood pressure. Mean arterial pressure was diastolic blood pressure plus one third of pulse pressure. The Expanded Methods in the online-only Data Supplement (pages S3–S5) provide a thorough description of the methods used for administering questionnaires, recording dietary habits, and the methods used for the biochemical measurements including blood lead.

Statistical Analysis

For database management and statistical analysis, we used SAS software, version 9.3 (SAS Institute Inc, Cary, NC). For variables that required a logarithmic transformation to approximate a normal distribution, including blood lead, serum cotinine, and γ-glutamyltransferase, and dietary calcium and caffeine, we reported the central tendency and spread of the data as the geometric mean and the interquartile range. Between-group comparisons of means relied on the standard normal z test or Tukey test for multiple comparisons. For between-group comparisons of proportions, we applied the χ^2 statistic test with Bonferroni correction of the significance levels if multiple groups were involved.

Details of the analysis plan and the statistical tests applied appear in the Expanded Methods in the online-only Data Supplement (pages S5–S6). In a first step of the analysis, we plotted mean values of systolic and diastolic blood pressure by deciles of the blood lead concentration for each of the 6 ethnicity-sex strata separately. Next, we searched for covariables significantly and independently associated with blood pressure in a stepwise regression procedure with P values for explanatory variables to enter and stay in the model set at 0.15. After having determined the standard set of covariables to adjust for, we computed for each ethnicity-sex stratum the multivariable-adjusted associations between blood pressure and blood lead. We tested between-group differences in these association by introducing the appropriate interaction terms with blood lead in the models.

Results

Characteristics of Participants by Ethnicity and Sex

The 12725 participants included 2692 (21.1%) blacks, 2607 (20.5%) Hispanics, 7426 (58.4%) whites, and 6199 (48.7%) women. The characteristics listed in Table 1 are significantly different between the 3 ethnic groups (P<0.0001) except for pulse pressure (P=0.66) and heart rate (P=0.30). The online-only Data Supplement includes a detailed description of the differences in the characteristics of participants by ethnicity (page S6) and sex (page S7). The blood lead concentration was lower (P<0.0001) among whites when compared with black and Hispanic participants (1.46 versus 1.57 μg/dL) with no difference (P=0.12) between Hispanics (1.55 μg/dL) and blacks (1.60 μg/dL). Women had a lower blood lead concentration than men had (1.25 versus 1.80 μg/dL; P<0.0001). When adjusted for hematocrit, the blood lead concentration remained lower in women than in men (1.29 versus 1.74 μg/dL; P<0.0001). Figure S1 in the online-only Data Supplement describes the distributions of blood lead by ethnicity and sex.

Unadjusted Analyses

The Figure shows that in the unadjusted analysis of the 6 ethnicity-sex strata, systolic blood pressure increased (P<0.0001) with higher blood lead concentration and that a linear model was adequate to describe the data. The corresponding associations with diastolic blood pressure were significantly positive (P≤0.018) or not significant (P≥0.33) but also suggested that a linear model accurately captured the data (Figure S2).

In unadjusted analyses of all participants, systolic and diastolic pressure increased (P<0.0001) with higher blood lead (Table S1). The effect sizes associated with a doubling of the blood lead concentration were 4.80 mm Hg (95% CI, 4.46–5.14) for systolic pressure and 0.67 mm Hg (CI, 0.45–0.89) for diastolic pressure (Table S1). Considering the six ethnicity-sex strata, systolic and diastolic pressure also increased with higher blood lead (P≤0.018), except for diastolic pressure (Table S1) in white women (P=0.69) and non-Black men (P≥0.33). In unadjusted analyses, pulse pressure and mean arterial blood pressure consistently increased (P≤0.0095) with blood lead in all ethnicity-sex strata and in all participants (Table S2, page S7).

Among all participants, 4893 (38.5%) had hypertension. The diagnosis of hypertension rested on a systolic pressure of ≥140 mm Hg in 1903 subjects, a diastolic pressure of ≥90 mm Hg in 228, an elevation of both systolic and diastolic pressure in 406, and the use of antihypertensive drugs in 2356 participants, in whom the aforementioned blood pressure criteria were not met. The unadjusted odds ratio for a doubling of the blood lead concentration (Table S3) was 1.58 (95% CI, 1.52–1.65) in all participants. Across the 6 ethnicity-sex strata, except for Hispanic men (P=0.12), the unadjusted odd ratios were significant (P<0.0001), ranging from 1.51 in Hispanic women to 2.17 in white women (Table S3).

Identification of Covariables

Covariables of systolic and diastolic pressure, as selected by stepwise regression, appear in Table 2. Age was the most important independent covariable, explaining 20.5% and 11.4% of the systolic and diastolic variance, respectively (Table 2). With whites as reference, both blacks and Hispanics

Table 1. Characteristics of Participants

	Women			Men		
Characteristic	Black	Hispanic	White	Black	Hispanic	White
No. in category	1346	1233	3620	1346	1374	3806
No. with characteristics (%)						
Current smoker	276 (20.5)	139 (11.3)	800 (22.1)	394 (29.3)	341 (24.8)	918 (24.1)
Drinking alcohol	69 (5.1)	33 (2.7)	255 (7.0)	228 (16.9)	311 (22.6)	812 (21.3)
Diabetes mellitus	230 (17.1)	222 (18.0)	367 (10.1)	222 (16.5)	218 (15.9)	485 (12.7)
On antidiabetic drugs	192 (14.3)	174 (14.1)	268 (7.4)	174 (12.9)	162 (11.8)	345 (9.1)
Hypertension	629 (46.7)	416 (33.7)	1383 (38.2)	573 (42.6)	382 (27.8)	1510 (39.7)
On antihypertensive drugs	518 (38.5)	294 (23.8)	1068 (29.5)	402 (29.9)	240 (17.5)	1123 (29.5)
Poverty index below threshold	303 (22.5)	387 (31.4)	506 (14.0)	237 (17.6)	405 (29.5)	424 (11.1)
High-school education	991 (73.6)	579 (47.0)	3030 (83.7)	963 (71.6)	597 (43.5)	3144 (82.6)
College graduate	231 (17.2)	101 (8.2)	903 (24.9)	201 (14.9)	99 (7.2)	1046 (27.5)
Mean of characteristic (±SD)						
Age, y	48.3±16.8	48.1±16.8	53.0±18.4	47.7±16.9	46.1±16.8	53.1±18.6
Body mass index, kg/m^2	31.5±7.8	29.8±6.1	28.1±6.9	28.8±6.5	28.6±5.0	28.5±5.8
Systolic pressure, mm Hg	125.6±20.7	123.0±20.9	122.6±20.4	127.5±17.3	124.5±17.2	125.2±16.7
Diastolic pressure, mm Hg	70.7±12.2	68.6±10.8	68.4±11.4	73.1±12.8	70.4±11.5	70.8±11.8
Mean arterial pressure, mm Hg	89.0±12.6	86.7±11.8	86.5±11.4	91.2±12.2	88.4±11.2	89.0±11.0
Pulse pressure, mm Hg	54.9±19.2	54.4±19.3	54.2±20.7	54.4±16.3	54.1±16.6	54.4±17.1
Heart rate, bpm	74.1±12.2	73.4±11.0	74.0±11.9	70.2±12.9	70.2±11.8	70.4±12.4
Hematocrit, %	38.2±3.7	39.4±3.5	40.2±3.3	43.3±3.7	45.1±3.4	44.5±3.7
Total cholesterol, mg/dL	194.3±40.6	199.3±40.4	203.1±42.0	192.4±41.8	200.8±41.7	193.1±41.0
Serum creatinine, mg/dL	0.83±0.20	0.69±0.16	0.81±0.19	1.07±0.20	0.90±0.18	1.01±0.19
Serum glucose, mg/dL	100.0±38.9	105.8±45.2	96.4±27.0	101.7±38.7	108.9±48.4	101.2±32.3
Serum protein, g/dL	7.30±0.49	7.28±0.43	7.01±0.42	7.37±0.51	7.36±0.46	7.10±0.44
Serum total calcium, mg/dL	9.49±0.39	9.38±0.37	9.47±0.37	9.55±0.38	9.45±0.34	9.49±0.35
Dietary sodium:potassium ratio	1.51±0.63	1.28±0.57	1.31±0.59	1.54±0.66	1.30±0.56	1.37±0.58
Geometric mean (IQR)						
Blood lead, μg/dL	1.37 (0.88–2.10)	1.21 (0.80–1.78)	1.22 (0.80–1.86)	1.86 (1.20–2.85)	1.94 (1.25–2.83)	1.73 (1.16–2.57)
Cotinine, ng/mL	0.57 (0.03–22.4)	0.07 (0.01–0.10)	0.27 (0.01–1.66)	1.77 (0.05–160)	0.27 (0.02–3.46)	0.74 (0.02–139)
γ-glutamyltransferase, units/L	21.7 (15.0–28.0)	20.0 (13.0–28.0)	18.2 (12.0–24.0)	28.6 (19.0–39.0)	29.4 (19.0–40.0)	24.5 (16.0–34.0)
Dietary calcium, g/d	0.55 (0.38–0.87)	0.68 (0.46–1.03)	0.72 (0.50–1.08)	0.67 (0.44–1.08)	0.80 (0.55–1.23)	0.90 (0.62–1.34)
Dietary caffeine, mg/d	18.6 (1.00–112)	32.6 (5.00–147)	74.2 (43.0–275)	23.4 (1.00–142)	48.7 (29.0–192)	101 (64.0–332)

Hypertension was a blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic or the use of antihypertensive drugs. Diabetes mellitus was a fasting or random blood glucose of ≥126 mg/dL or ≥200 mg/dL, respectively, the use of antidiabetic drugs, or a self-reported diagnosis. IQR indicates interquartile range

had higher systolic pressure (Table 2). Blacks also had higher diastolic pressure (Table 2). Systolic pressure was inversely associated with heart rate, whereas the opposite was the case for diastolic pressure. Both systolic and diastolic pressure significantly ($P \leq 0.0035$) and independently increased with body mass index, γ-glutamyltransferase as index of alcohol intake, hematocrit and the dietary sodium:potassium ratio. Users of antihypertensive drugs had higher blood pressure. Diastolic pressure was independently and inversely correlated with serum cotinine. College graduation was associated with lower systolic and diastolic pressure. Taken together, all covariables selected explained 25.7% of systolic pressure and 17.9% of diastolic pressure.

The online-only Data Supplement (Table S4, page S8) shows that the covariables associated in stepwise regression with pulse pressure and mean arterial pressure were similar as those correlated with systolic and diastolic pressure and together explained 35.6% of pulse pressure and 14.8% of mean arterial pressure. On the basis of above results, we adjusted all regression models relating blood pressure components to blood lead for ethnicity and sex (as appropriate), the linear and squared terms of age, body mass index, heart rate, hematocrit, serum total calcium, γ-glutamyltransferase and cotinine, the dietary sodium:potassium intake ratio, attainment of a college grade, and antihypertensive drug treatment.

Multivariable-Adjusted Association of Blood Pressure With Blood Lead

Among women, the multivariable-adjusted associations between systolic and diastolic pressure and blood lead

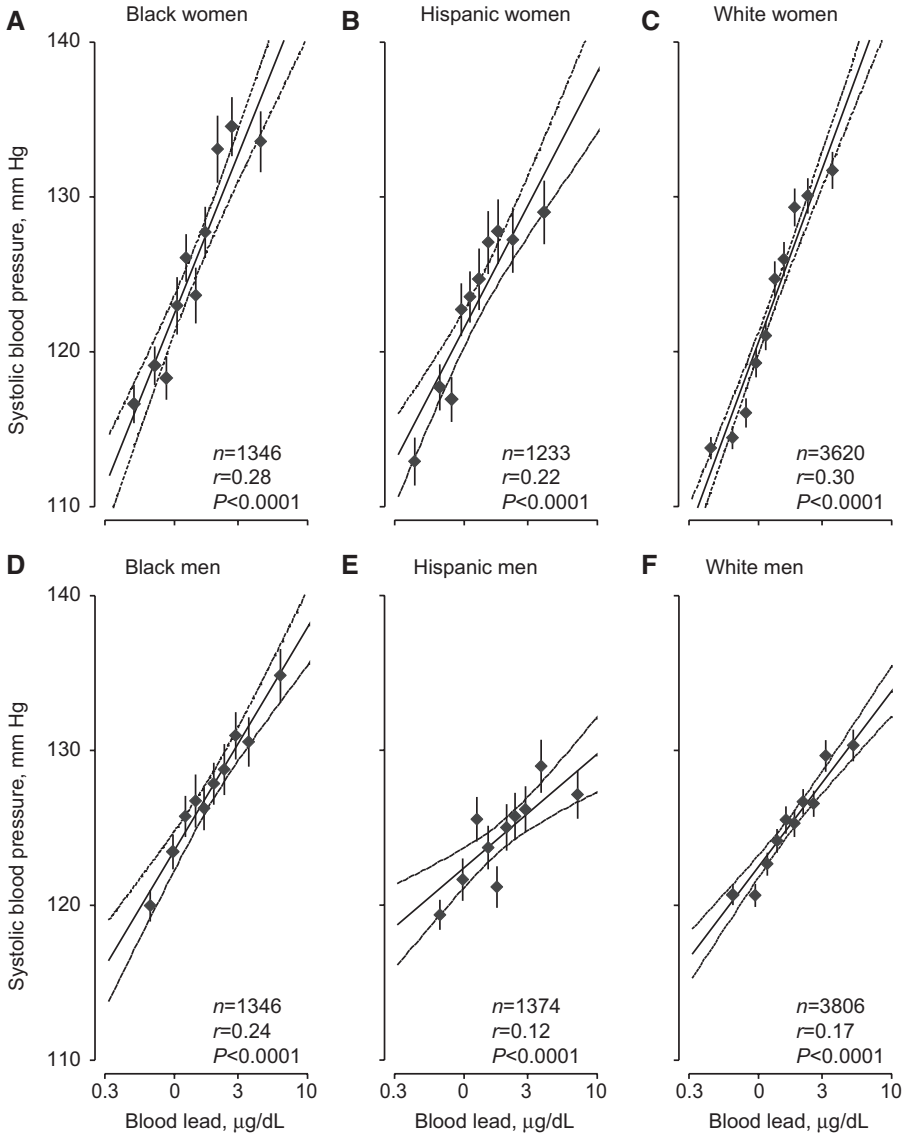

Figure. Unadjusted associations between systolic blood pressure and blood lead by ethnicity-sex strata. The regression line with 95% confidence interval was computed using the individual subjects in each stratum. The dots plotted over the regression line represent the means of systolic blood pressure and lead in each decile of the ethnicity- and sex-specific distributions. Vertical bars denote the SE of systolic blood pressure. The Figure confirmed the adequacy of the linear model in addition to the statistical tests described in the Methods section of this article.

(Table 3) did not reach significance in any of the ethnic groups ($P \geq 0.090$), except for diastolic pressure in white women, which was +0.73 mm Hg higher (95% CI, +0.23 to +1.24; $P=0.0045$) for a 2-fold increase in blood lead. In all women combined, the effect sizes associated with a doubling of the blood lead concentration were +0.58 mm Hg (95% CI, +0.01 to +1.17; $P=0.050$) for systolic pressure and +0.43 (95% CI, 0.07 to +0.80; $P=0.021$) for diastolic pressure. Among men, systolic pressure was significantly and independently associated with the blood lead concentration in black and Hispanic men ($P \leq 0.038$), whereas the corresponding association in white men was statistically weaker ($P=0.060$). The effect sizes for a doubling of the blood lead concentration ranged from +1.61 mm Hg in blacks to +0.65 mm Hg in whites. In all men combined, the effect size was +0.79 mm Hg (95% CI, +0.30 to +1.27; $P=0.0015$). The relationship between diastolic pressure and blood lead did not reach formal significance ($P \geq 0.062$) among black and Hispanic men. In white men, diastolic pressure was significantly and positively associated with blood lead (effect size, +0.70 mm Hg; 95% CI, +0.24 to +1.17; $P=0.0032$). Among all participants, for each 2-fold increase in the blood lead concentration, blood pressure components increased, by +0.76 mm Hg (95% CI, +0.38 to +1.13; $P<0.0001$) for systolic pressure and by +0.43 mm Hg (95% CI, +0.18 to +0.68; $P=0.0007$) for diastolic pressure (Table 3).

For systolic blood pressure, all interaction terms of ethnicity and sex with blood lead were significant ($P \leq 0.019$). For diastolic pressure, the interaction terms of ethnicity and sex with lead were nonsignificant ($P \geq 0.17$), except for the interaction between Hispanic ethnicity and blood lead in relation to diastolic blood pressure. This interaction indicated that for a doubling of blood lead the increase in diastolic pressure among Hispanics was 0.70 mm Hg less (−1.20 to −0.20 mm Hg; $P=0.0057$) than in the other ethnicities.

The online-only Data Supplement gives full information on the multivariable-adjusted associations of pulse pressure and mean arterial pressure with blood lead in all participants and

Table 2. Correlates of Blood Pressure Components

	Systolic Blood Pressure, mm Hg			Diastolic Blood Pressure, mm Hg		
Covariables	Effect Size (95% CI)	r^2 (%)	*P* Value	Effect Size (95% CI)	r^2 (%)	*P* Value
Black vs white (1,0)	3.98 (3.22 to 4.74)	0.81	<0.0001	2.20 (1.71 to 2.70)	0.87	<0.0001
Hispanic vs white (1, 0)	2.14 (1.38 to 2.89)		<0.0001	–1.27 (–1.78 to –0.77)		<0.0001
Age (+18.0 y)	–0.27 (–2.05 to 1.50)	20.5	0.76	21.4 (20.3 to 22.6)	11.4	<0.0001
Age^2 (+1875 y^2)	8.18 (6.41 to 9.95)		<0.0001	–22.4 (–23.5 to –21.2)		<0.0001
Body mass index (+6.5 kg/m^2)	1.28 (0.98 to 1.59)	0.37	<0.0001	0.43 (0.23 to 0.63)	0.17	<0.0001
Heart rate (+12.2 bpm)	–0.53 (–0.82 to –0.24)	0.07	0.0004	1.31 (1.12 to 1.50)	1.35	<0.0001
γ-glutamyltransferase (×2)	1.78 (1.45 to 2.11)	1.77	<0.0001	0.59 (0.37 to 0.80)	0.26	<0.0001
Cotinine (×2)	…	…	…	–0.18 (–0.21 to –0.14)	0.53	<0.0001
Hematocrit (+4.3%)	1.14 (0.84 to 1.44)	0.44	<0.0001	2.42 (2.22 to 2.62)	3.23	<0.0001
College graduate (1, 0)	–2.59 (–3.32 to –1.86)	0.28	<0.0001	–0.50 (–0.99 to –0.01)	0.03	0.047
Antihypertensive drugs (1, 0)	4.32 (3.59 to 5.05)	1.26	<0.0001	0.48 (–0.01 to 0.96)	0.02	0.051
Dietary sodium:potassium ratio (+0.60)	0.45 (0.16 to 0.75)	0.05	0.0027	0.29 (0.10 to 0.48)	0.06	0.0035
Serum total calcium (+0.37 mg/dL)	0.73 (0.44 to 1.03)	0.12	<0.0001	…	…	…
Total explained variance (R^2)	...	25.7	...	...	17.9	...

Effect sizes (95% CI) express the multivariable-adjusted change in blood pressure associated with the explanatory variables, as category, on a linear scale (+1-SD), or on a logarithmic scale (doubling). The explanatory variables were selected by a stepwise regression procedure with the *P* values for variables to enter and stay in the models set at 0.15. The linear and squared terms of age, as well as the design variables coding for ethnicity, were offered together for entry into the model. An ellipsis indicates that a variable did not enter the model. Variables considered that did not enter in any model were sex, dietary intake of calcium and caffeine, and the poverty index ratio. R^2 and r^2 indicate the variance explained in percentage by the whole model or by single or sets of variables. CI indicates confidence interval.

in the 6 ethnicity-sex strata (Table S5, pages S8–S9). Among all participants, mean arterial pressure was 0.54 mm Hg higher (95% CI, 0.29–0.79; $P<0.0001$) for each 2-fold increase in the blood lead concentration, whereas there was no significant association between pulse pressure and blood lead even when all participants were pooled (Table S5). For pulse pressure, interactions of ethnicity and sex with blood lead were all significant ($P\leq0.027$). For mean arterial pressure, all interaction terms of ethnicity and sex with blood lead were nonsignificant ($P\geq0.096$).

Multivariable-Adjusted Risk of Hypertension in Relation to Blood Lead

The odds of having hypertension associated with a doubling of the blood lead concentration (Table 4) only reached formal significance in black women ($P=0.049$) and Hispanic men ($P=0.042$), in whom the odds ratios were 0.82 (95% CI, 0.67–0.99) and 0.84 (CI, 0.71–0.99), respectively. For all other subgroups, the odds ratios were not statistically significant ($P\geq0.12$). Among all participants, the odds ratio was 0.95 (95% CI, 0.90–1.01; $P=0.11$).

Table 3. Multivariable-Adjusted Association of Blood Pressure Components with Blood Lead

	Systolic Blood Pressure, mm Hg			Diastolic Blood Pressure, mm Hg		
Strata by Ethnicity and Sex	Effect Size (95% CI)	r^2, %	*P* Value	Effect Size (95% CI)	r^2, %	*P* Value
Women						
Black (n=1346)	1.18 (–0.19 to 2.55)	0.16	0.090	0.52 (–0.34 to 1.37)	0.09	0.24
Hispanic (n=1233)	0.56 (–0.57 to 1.69)	0.05	0.33	–0.13 (–0.81 to 0.55)	>0.00	0.71
White (n=3620)	0.61 (–0.18 to 1.40)	0.04	0.13	0.73 (0.23 to 1.24)	0.19	0.0045
All women (n=6199)	0.58 (0.01 to 1.17)	0.04	0.050	0.43 (0.07 to 0.80)	0.07	0.021
Men						
Black (n=1346)	1.61 (0.45 to 2.76)	0.46	0.0066	0.81 (–0.04 to 1.66)	0.21	0.062
Hispanic (n=1374)	0.95 (0.05 to 1.84)	0.24	0.038	–0.03 (–0.64 to 0.58)	>0.00	0.92
White (n=3806)	0.65 (–0.03 to 1.32)	0.08	0.060	0.70 (0.24 to 1.17)	0.18	0.0032
All men (n=6526)	0.79 (0.30 to 1.27)	0.13	0.0015	0.47 (0.13 to 0.81)	0.09	0.0072
All participants (n=12725)	0.76 (0.38 to 1.13)	0.09	<0.0001	0.43 (0.18 to 0.68)	0.07	0.0007

Effect sizes (95% CI) express the multivariable-adjusted change in blood pressure associated with a doubling of the blood lead concentration. Estimates were adjusted for ethnicity and sex (as appropriate), the linear and squared terms of age, body mass index, heart rate, hematocrit, serum total calcium, γ-glutamyltransferase and cotinine, the dietary sodium:potassium intake ratio, college education, and antihypertensive drug treatment. CI indicates confidence interval.

Table 4. Adjusted Association Between Hypertension and Blood Lead

Strata by Ethnicity and Sex	Odds Ratio (95% CI)	*P* Value
Women		
Black (n=1346)	0.82 (0.67–0.99)	0.049
Hispanic (n=1233)	0.86 (0.72–1.04)	0.12
White (n=3620)	1.06 (0.94–1.21)	0.33
All women (n=6199)	0.95 (0.87–1.04)	0.26
Men		
Black (n=1346)	1.00 (0.84–1.20)	0.97
Hispanic (n=1374)	0.84 (0.71–0.99)	0.042
White (n=3806)	0.99 (0.89–1.10)	0.78
All men (n=6526)	0.95 (0.87–1.02)	0.17
All participants (n=12725)	0.95 (0.90–1.01)	0.11

Effect sizes (95% CI) express the multivariable-adjusted risk of having hypertension associated with a doubling of the blood lead concentration. Odds ratios were adjusted for ethnicity and sex (as appropriate), the linear and squared terms of age, body mass index, heart rate, hematocrit, serum total calcium, γ-glutamyltransferase and cotinine, college education, and the dietary sodium:potassium intake ratio. CI indicates confidence interval

Sensitivity Analyses

The sensitivity analyses (Tables S6–S8, pages S9–S10) confirmed the primary findings.

Discussion

We undertook our current study in view of the steadily declining blood lead levels in the United States. The blood lead concentration averaged 13.1 μg/dL[1] in NHANES II (1976–1980), declined to 2.76 μg/dL in NHANES III (1988–1994),[3] and to 1.64 μg/dL and 1.41 μg/dL in NHANES IV (1999–2002[3] and 2005–2006[8]). In our present study (2003–2010), the mean blood lead concentration was 1.51 μg/dL. The key findings can be summarized in 4 points. First, across 6 ethnicity-sex strata, the relationship between the blood pressure components was inconsistent, usually with larger effects sizes among men than women and among blacks than non-blacks. Second, the effect sizes, although significant for systolic, diastolic, and mean arterial pressure in pooled analyses of all women and men combined, were all smaller than 0.79 mm Hg. Third, pulse pressure was not related to blood lead, except for a weak association in Hispanic men. Fourth, the small effect sizes explain why overall the odds of having hypertension was not associated with the blood lead concentration.

A comprehensive review of previous studies of the association of blood pressure or the prevalence of hypertension with lead exposure[3,4,8] is beyond the scope of this article but is available in the online-only Data Supplement (pages S10–S12). The current literature shows discrepancy between studies in populations and workers. The explanations that are commonly put forward for this apparent discrepancy are the higher statistical power in large epidemiological surveys relative to smaller occupational cohorts and selection bias, often referred to as the healthy worker effect. Considering the available literature, NHANES is undoubtedly the most appropriate data source to address the issue of the potential association of blood pressure or hypertension with environmental lead exposure. NHANES conducted by the National Center for Health Statistics is the principal resource for tracking progress in reducing lead in the environment. Because NHANES surveyed a large probability sample of the general population, the findings can be generalized to the United States as a whole. Moreover, individuals with high exposure or at risk of high exposure were excluded from the NHANES sample. Previous NHANES phases showed a substantial decline in blood lead levels.[1,3,8] The percentage of adults with blood lead level of 10 μg/dL or higher was as low as 0.7% in 1999 to 2002.[3]

Two previous NHANES IV studies reported on the association of blood pressure or the risk of hypertension with blood lead.[3,8] Both studies confirmed that blood lead levels continue to decline among adults in United States, but that racial and ethnic disparities persist.[3,8] One study reported that blood lead levels were significantly associated with higher systolic blood pressure among black men and women, but not among white or Mexican-American participants, and that blood lead was significantly correlated with higher diastolic blood pressure among white men and women and black men, whereas a negative association was observed in Mexican-American men.[8] The second study reported that blood lead levels remained associated with a higher burden of chronic kidney disease and peripheral arterial disease.[3] Our current analysis essentially showed that the low levels of lead that exist today in the United States have little influence on blood pressure. Our analytic approach also differed from the 2 previously published reports in several aspects. First, in unadjusted analyses, we tested the adequacy of the linear model to describe the relationship between blood pressure and blood lead. Second, in our multivariable-adjusted analyses, we analyzed blood lead as a continuous variable instead of examining the linear trend across quartiles[3] or contrasting the bottom with the top decile.[8] Third, we analyzed both the pulsatile components (systolic pressure and pulse pressure) and the steady components (diastolic pressure and mean arterial pressure) of blood pressure. Our observation that pulse pressure was unrelated to blood lead is at variance with studies relating peripheral arterial disease or cardiovascular disease with lead exposure.[9,10] However, smoking was a major confounder in these reports.[9,10] Fourth, we adjusted for a large number of covariables, including aspects of lifestyle that previous NHANES studies[3,8] did not consider, such as nutritional factors, social status, and serum cotinine and γ-glutamyltransferase, as biomarkers of smoking and drinking alcohol.

Our current study must be interpreted within the context of its limitations. First, the cross-sectional nature of our current analysis does not allow to make any causal interferences about the association between blood pressure and the prevalence of hypertension in relation to lead exposure. Second, we cannot ascertain that we accounted for all confounders, in particular, when we assessed the association between blood pressure and blood lead across 6 ethnicity-sex strata. Third, blood pressure was the average of 3

conventional blood pressure readings. Out-of-the-office blood pressure measurement by ambulatory monitoring or self-measurement at home is the current state of the art to assess blood pressure.[11] Fourth, a potential limitation of our study was that we did not measure bone lead as exposure marker. Approximately 95% of the total body burden of lead is present in the skeleton, and measurement of bone lead levels can provide a more reliable measure of the internal dose.[12] Some investigators reported that hypertension was associated with bone lead, but not with blood lead.[13,14] A possible drawback of using bone lead as exposure index is that bone levels increase with age, as blood pressure does, making it difficult to correct for age effects. Furthermore, the upper end of bone lead levels reported in previous studies[13,14] was characteristic of occupational rather than environmental exposure. Blood lead reflects both recent exogenous exposure and endogenous redistribution of the lead stored in bone, but may underestimate the internal dose of lead.

Perspectives

In our current study, the increase from the low to high end of the distribution was ≈10-fold. The 5th to 95th percentile interval encompassed 0.54 and 4.35 μg/dL. In the unlikely event that a patient would move from the bottom to the top of the blood lead distribution, which would translate in a maximum increase in blood pressure by ≈5 mm Hg systolic or ≈3 mm Hg diastolic. Furthermore, in our current cross-sectional analysis, there was no consistent relationship of the blood pressure level or the prevalence of hypertension with the blood lead concentration. The association between hypertension and blood lead was not significant. Accordingly, lead exposure within the range studied might not entail any excess morbidity or mortality attributable to hypertension and its cardiovascular complications.[15] However, more prospective population studies with assessment of both fatal and nonfatal cardiovascular end points are required to confirm this assertion. The currently available prospective population studies[15–19] are contradictory, reporting positive[16–19] or null[15] associations between outcome and lead exposure, but to our knowledge only 2[15,16] accounted for both fatal and nonfatal events. Not having the nonfatal outcomes in an era when invasive cardiologist remove obstructions and restore patency of coronary arteries, when coronary bypass surgery became a low-risk procedure, and when stroke units are delivering specialized intensive care, recording the nonfatal events should become the state of the art. Finally, for now, no study captured the low end of the exposure–response relationship for blood lead levels and end points of cardiovascular function in lead workers. Therefore, studies specifically addressing these issues in a longitudinal follow-up of lead exposed workers who will go from no previous occupational (general population blood lead levels) to occupational lead exposures are needed.

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Disclosures

None.

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Novelty and Significance

What Is New?

- In the United States, the National Health and Nutrition Examination Survey documented a progressive decline in blood lead. National Health and Nutrition Examination Survey III (1988–1994) documented ethnic diversity in the association of blood pressure with blood lead. Therefore, we analyzed 12 725 people included in the National Health and Nutrition Examination Survey IV (2003–2010) database.

What Is Relevant?

- The association between blood pressure components and blood lead was inconsistent across 6 strata based on ethnicity (blacks, Hispanics, and whites) and sex.
- Among 6199 women, the adjusted effect sizes associated with a doubling of blood lead were +0.58 mm Hg (P=0.05) systolic and +0.43 (P=0.021) diastolic.
- Among 6526 men, the corresponding effect sizes were +0.79 mm Hg (P=0.0015) and +0.47 (P=0.0072), respectively.
- Among all participants, the odds ratio for hypertension associated with a doubling of blood lead was 0.95 (P=0.11).

Summary

At the currently declining exposure levels, associations of blood pressure with blood lead were inconsistent across the ethnicity-sex strata. The effect sizes, although significant in pooled analyses of all women and men, were smaller than 0.79 mm Hg and likely exclude current environmental lead exposure in the United States as a clinically meaningful cause of hypertension.

HYPERTENSION

Expanded Methods and Data Supplement

Blood Pressure in Relation to Environmental Lead Exposure in the National Health and Nutrition Examination Survey 2003–2010

Short title: Blood Pressure and Lead Exposure

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Expanded Methods

Field Work

The United States (US) National Center for Health Statistics (NCHS: Centers for Disease Control and Prevention, Atlanta, GA) conducted NHANES IV (1999–2012). NHANES consists of cross-sectional, nationally representative surveys of the non-institutionalized civilian population of the US. The survey employs a multistage stratified probability sample based on selected counties, blocks, households, and persons within households. Certain subgroups of the population, such as Mexican Americans, black non-Hispanics, and older adults were oversampled to improve the precision of estimates for these groups. Interviews were conducted at the participants' homes. The comprehensive physical examinations, which included measurements of anthropometric characteristics, blood pressure and collection of blood and urine samples took place at mobile exam centers (MEC). The NCHS Institutional Review Board approved the interviews, physical examinations, and the procedure to obtain written informed consent.

Selection of Participants

The NHANES IV data considered for the current analysis were collected in seven stages, 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012. From the NHANES IV database available online, we downloaded and pooled 80 datasets containing information on anthropometric characteristics, biochemical measurements, lifestyle, dietary habits, socio-economic status, and the blood lead concentration. The pooled data initially comprised 71,916 people examined from 1999 until 2012. Of those, we excluded 3211, because they did not undergo the physical examination. We furthermore removed from analysis 32,634 participants younger than 20 years, 4766 whose ethnicity was undetermined, and 1324 women who were either pregnant (n=1114) or breast-feeding (n=210).

In keeping with our previous report,[1] we planned to account for dietary habits. This forced us to exclude 8111 participants examined from 1999 until 2002, because the protocol for collecting dietary information substantially changed in 2002 and a further 3814 people examined in 2011 and 2012, because dietary information was lacking in the online database. We had to disregard an additional 5193 participants because of missing covariables required for the present analysis. Finally, we excluded participants with extremely elevated values (in excess of the mean plus 3 SDs) of serum creatinine (n=102), the dietary sodium-to-potassium ratio (n=27), and dietary calcium (n=5) or caffeine (n=4) intake. Thus, the number of subjects analyzed totaled 12,725. For analysis, self-reported ethnicity was categorized as non-Hispanic White, non-Hispanic Black, and Hispanic.

Compared with the 17,066 excluded adults whose ethnicity was undetermined or who had no blood pressure data, the 12,725 analyzed adults were older (49.4 *vs.* 50.8 years), had lower systolic blood pressure (125.9 *vs.* 124.5 mm Hg) and included fewer Blacks (25.5% *vs.* 21.2%), Hispanics (22.6% *vs.* 20.5%), and women (53.0% *vs.* 48.7%). All P-values for these comparisons were less than 0.0001. However, diastolic blood pressure did not differ between excluded and included adults (70.1 *vs.* 69.8 mm Hg; P =0.068).

Measurements

The questionnaires administered at home and MEC provided detailed information on each participant's medical history, use of drugs, smoking and drinking habits, lifestyle, educational achievement, and socio-economic status. Participants who reported using smoking materials some days or every day or consuming at least one drink per week were categorized as smokers and drinkers, respectively. At MEC, trained observers measured anthropometric characteristics and blood pressure and administered the questionnaire on dietary habits.

Following the guidelines of the American Heart Association, the observers measured each person's blood pressure on the right arm to the nearest 2 mm Hg with a standard mercury sphygmomanometer by auscultation of the Korotkoff sounds after participants had rested in the seated position for at least 5 minutes. Three cuff sizes were used depending on arm circumference: adult size if arm circumference was 22 to 29.9 cm (bladder width × length, 12 × 22 cm); large adult size if arm circumference was 30 to 37.9 cm (15 × 32 cm); and adult thigh size if arm circumference was 38 to 47.9 cm (18 × 35 cm).[2-5] Observers counted heart rate over 30 seconds. Blood pressure was the average of up to three readings. The number of blood pressure readings available for analysis was three in 11,601 participants (91.2%), two in 626 (4.9%) and only one in 498 (3.9%). Hypertension was a blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or use of antihypertensive drugs. Pulse pressure was the difference of systolic minus diastolic blood pressure. Mean arterial pressure was diastolic blood pressure plus one third of pulse pressure. Information on diet rested on a 24-h dietary recall and nutrient values assigned to foods according to the US Department of Agriculture (USDA) Food and Nutrient Database for Diet Studies. As described in detail elsewhere,[6] trained interviewers administered the 24-h dietary recalls, using an automated 5-stage computer-aided approach. Sodium from table salt and sodium and potassium from supplements and antacids were not included in the estimates of intake.

Measurements on blood included hematocrit; serum creatinine, cholesterol, glucose, total calcium, and protein; serum cotinine and γ-glutamyltransferase as biomarkers of smoking and drinking alcohol; and the blood lead concentration. Diabetes was the use of antidiabetic drugs, a fasting blood glucose concentration of at least 126 mg/dL, a random blood glucose concentration of at least 200 mg/dL, or a self-reported diagnosis.[7] Serum cotinine was measured by means of using an isotope dilution high performance liquid chromatography / atmospheric pressure chemical ionization tandem mass spectrometry method. The detection limit was 0.015 ng/mL. Blood lead was determined by the Centers for Disease Control and Prevention's National Center for Environmental Health, Division of Laboratory Sciences using inductively coupled plasma mass spectrometry. The detection limit was 0.28 µg/dL in NHANES IV (2003–2004) and 0.25 µg/dL in NHANES IV (2005–2010).[8] The detection of limit is the level at which the measurement has a 95% probability of being greater than zero.[9] Samples below the detection limit, 21 from 2003 to 2006 and 7 from 2007 to 2010 were assigned the limit of detection divided by the square root of 2.

Analysis Plan

In a first step of the analysis, we plotted mean values of systolic and diastolic blood pressure by deciles of the blood lead concentration for each of the six ethnicity-sex strata separately. We checked the linearity of the relation between blood pressure and log blood lead by plotting the cumulative Martingale residuals against log blood lead and computing the *P*-value of a Kolmogorov-type supremum test based on a sample of 1000 residual patterns. We implemented this check using the ASSESS statement in the PROC GENMOD procedure of the SAS software.

Next, we searched for covariables significantly and independently associated with blood pressure in a stepwise regression procedure with *P*-values for explanatory variables to enter and stay in the model set at 0.15. We considered the following explanatory variables: ethnicity, sex, age, body mass index, heart rate, hematocrit, calcium, γ-glutamyltransferase and cotinine, the dietary sodium-to-potassium intake ratio, dietary intake of calcium and caffeine, education and the poverty index ratio, and antihypertensive drug treatment. The linear and squared terms of age as well as the design variables coding for ethnicity were offered together for entry into the regression model. We also considered models in which the bi-

omarkers serum γ-glutamyltransferase and cotinine were substituted by reported alcohol intake and smoking, respectively. Finally, after having determined the standard set of covariables to adjust for, we computed for each ethnicity-sex stratum the multivariable-adjusted associations between blood pressure and blood lead. We tested between-group differences in these association by introducing the appropriate interaction terms with blood lead in the models. In sensitivity analyses, we additionally adjusted for the serum creatinine concentration and the presence of diabetes mellitus or we replaced the biomarkers of alcohol intake and exposure to tobacco smoke, by questionnaire data on drinking and smoking habits.

Results

Characteristics of Participants by Ethnicity and Sex

Whites compared with Blacks and Hispanics, were older (53.1 *vs.* 47.5 years) and had lower γ-glutamyltransferase (21.2 *vs.* 24.7 units/L), serum protein (7.06 *vs.* 7.33 g/dL) and a lower prevalence of diabetes (11.5% *vs.* 16.8%) and antidiabetic drug use (8.3% *vs.* 13.2%) with no differences in these measurements between Blacks and Hispanics ($P \geq 0.077$). Blacks compared with Hispanics and Whites had higher systolic (126.5 *vs.* 123.9 mm Hg), diastolic (71.9 *vs.* 69.6 mm Hg) and mean arterial pressure (90.1 *vs.* 87.7 mm Hg), lower hematocrit (40.8% *vs.* 42.4%) and total cholesterol (193.4 *vs.* 198.5 mmol/L), and less frequently reported alcohol intake (11.0% *vs.* 13.6%) with no differences in these variables between Hispanics and Whites ($P \geq 0.070$). Hispanics compared with Whites and Blacks had lower glucose (107.4 *vs.* 99.4 mg/dL) and included fewer smokers (18.4% *vs.* 23.6%) with no differences in these variables between Whites and Blacks ($P \geq 0.058$).

Women compared with men ($P < 0.0001$) had higher body mass index (29.2 *vs.* 28.6 kg/m^2) and heart rate (73.9 *vs.* 70.3 beats per minute), but lower systolic pressure (123.3 *vs.* 125.5 mm Hg), diastolic pressure (68.9 *vs.* 71.2 mm Hg) and mean arterial pressure (87.1 *vs.* 89.3 mm Hg). Compared with men ($P < 0.0001$), women also had lower hematocrit (39.6 *vs.* 44.4%) and lower serum levels of total cholesterol (194.6 *vs.* 200.5 mg/dL), creatinine (0.79 *vs.*1.00 mg/dL), glucose (99.0 *vs.*102.9 mg/dL), protein (7.13 *vs.* 7.21 g/dL), total calcium (9.45 *vs.* 9.49 mg/dL), γ-glutamyltransferase (19.2 *vs.* 26.3 units/L) and cotinine (0.25 *vs.* 0.72 ng/mL). Women compared with men ($P \leq 0.0069$), had lower dietary values of the sodium-to-potassium ratio (1.35 *vs.* 1.39) and intake of calcium (0.67 *vs.* 0.82 g/day) and caffeine (46.7 *vs.* 64.2 mg/day), less frequently reported smoking (19.6 *vs.* 25.3%) and drinking (5.8 *vs.* 20.7%), but had a higher frequency of antihypertensive drug use (30.3 *vs.* 27.1%), poverty index ratio below threshold (19.3 *vs.* 16.3 %) and high-school education attainment (74.2 *vs.* 72.1%). Age (50.8 years) and pulse pressure (54.4 mm Hg) and the prevalence of hypertension (38.5%), diabetes (13.7%), use of antidiabetic drugs (10.3%) and attaining a college graduate degree or above (20.3%) were similar among women and men ($P \geq 0.11$).

Pulse Pressure and Mean Arterial Pressure in Relation to Blood Lead

Unadjusted Analyses

In unadjusted analyses of all participants, pulse pressure and mean arterial blood pressure as well as systolic and diastolic pressure increased ($P < 0.0001$) with higher blood lead (Table S2). The effect sizes associated with a doubling of the blood lead concentration were 4.13 mm Hg (95% confidence interval [CI], 3.79 to 4.47) for pulse pressure and 2.04 (CI, 1.83 to 2.26) for mean arterial pressure (Table S2). These findings were consistent across the six ethnicity-sex strata ($P \leq 0.0095$).

Identification of Covariables
Covariables of pulse pressure and mean arterial pressure, as selected by stepwise regression, appear in Tables S4. Age was the most important independent covariable, explaining 31.7% and 8.02% of the variance in pulse pressure and mean arterial pressure (Table S4). With Whites as reference, both Blacks and Hispanics had higher pulse pressure (Table S4). Blacks also had higher mean arterial pressure (Table S4). Pulse pressure was inversely associated with heart rate, whereas the opposite was the case for mean arterial pressure. Both pulse pressure and mean arterial pressure significantly ($P \leq 0.0014$) and independently increased with body mass index, γ-glutamyltransferase as index of alcohol intake, and serum total calcium. Users of antihypertensive drugs had higher blood pressure. Mean arterial pressure increased with the hematocrit and the dietary sodium-to-potassium ratio. Mean arterial pressure was independently and inversely correlated with serum cotinine, whereas the association of cotinine with pulse pressure was positive. College graduation was associated with lower pulse pressure and mean arterial pressure. Taken together, all covariables selected explained 35.6% of pulse pressure and 14.8% of mean arterial pressure.

Multivariable-Adjusted Analyses
Among women, the multivariable-adjusted associations between pulse pressure and mean arterial pressure and blood lead (Table S5) did not reach significance in any of the ethnic groups ($P \geq 0.11$), except for mean arterial pressure in White women, which for a twofold increase in blood lead was +0.69 mm Hg higher (CI, +0.18 to +1.21; $P=0.0081$). In all women combined, the effect sizes associated with a doubling of the blood lead concentration were +0.15 (CI, –0.37 to +0.67; $P=0.57$) for pulse pressure and +0.48 mm Hg (CI, +0.10 to +0.86; $P=0.012$) for mean arterial pressure. Among men, mean arterial pressure was significantly and independently associated with the blood lead concentration in Black and White men ($P \leq 0.010$), whereas the corresponding association in Hispanic men was not significant ($P=0.33$). The effect sizes for a doubling of the blood lead concentration ranged from +1.08 mm Hg in Blacks to +0.68 mm Hg in Whites. In all men combined, the effect size was +0.57 mm Hg (CI, +0.24 to +0.91; $P=0.0007$). The relation between pulse pressure and blood lead did not reach formal significance ($P \geq 0.14$) among Black and White men and in all ethnic groups combined, although pulse pressure was significantly associated with the blood lead concentration in Hispanic men, in whom the effect size was +0.98 mm Hg (CI, +0.14 to +1.82; $P=0.023$).

Among all participants, mean arterial pressure was 0.54 mm Hg higher (CI, 0.29 to 0.79; $P<0.0001$) for each twofold increase in the blood lead concentration, whereas there was no significant association between pulse pressure and blood lead even when all participants were pooled (Table S5). For pulse pressure, interactions of ethnicity and sex with the blood lead concentration were all significant ($P \leq 0.027$). For mean arterial pressure components, all interaction terms of ethnicity and sex with the blood lead concentration were nonsignificant ($P \geq 0.096$).

Sensitivity Analyses
If we additionally adjusted for serum creatinine concentration and the presence of diabetes mellitus (Tables S6, S7 and S8) or if we replaced γ-glutamyltransferase and cotinine, biomarkers of alcohol consumption and smoking, by questionnaire data (data not shown), our results did not materially change. Our result also remained consistent with 3645 participants on antihypertensive drug treatment excluded (data not shown).

Worse renal function might affect the renal excretion of blood lead and might therefore lead to a higher blood lead concentration. In an unadjusted model involving all participants,

the simple correlation coefficient between blood lead and serum creatinine was 0.27 (P<0.0001). Each 1-SD (0.22 mg/dL) increment in serum creatinine was associated with a 18.6% higher blood lead concentration (CI, 17.3 to 19.9%; P<0.0001). With adjustments applied for ethnicity, sex, the linear and square terms of age, mean arterial pressure, body mass index, serum γ-glutamyltransferase and cotinine, diabetes, and use of antihypertensive drugs, this estimate was 4.73% (CI, 3.55 to 5.94%; P<0.0001).

Discussion

Summary of Previous NHANES IV Findings

Two previous NHANES IV studies reported on the association of blood pressure or the risk of hypertension with blood lead.[10,11] Both studies reported inconsistent associations across strata defined by ethnicity and sex. Based on NHANES data IV (1999–2002), Muntner and colleagues reported that with multivariable adjustments applied persons in the highest quartile of blood lead (≥2.47 μg/dL) compared with those in the lowest quartile (<1.06 μg/dL) were 2.72 and 1.92 times more likely (*P*-value for trend <0.001) to have chronic kidney disease and peripheral arterial disease. However, the trend of the adjusted odds ratios for hypertension with increasing category of blood lead was weak, being nonsignificant in Whites (*P*=0.61), and marginally significant in Blacks (*P*=0.06) and Hispanics (*P*=0.04). Scinicariello and colleagues assessed the relation between blood pressure outcomes and blood lead among people with a blood lead level below 10 μg/dL, using data from the NHANES IV (1999–2006) stratified by ethnicity and sex.[11] There was a multivariable-adjusted positive association between systolic blood pressure and blood lead among Black women and men, but not in White or Hispanic participants. Diastolic blood pressure was significantly associated with blood lead among White women and men and Black men, whereas a negative association was observed in Hispanic men. Black men in the top decile of the blood lead distribution (≥3.5 μg/dL) compared with Black men in the bottom decile (≤0.7 μg/dL) had a significantly increased risk of having hypertension, while no significant association was observed in any other of the ethnicity-sex groups.[11]

Meta-analyses

Two meta-analyses of summary statistics[12,13] addressed the association between blood pressure[12] or hypertension[12,13] with lead exposure as quantified from blood[12,13] or bone[13] lead. In our own meta-analysis based on 58,518 subjects, recruited from the general population in 19 surveys and from occupationally exposed groups in 12 studies, the association between blood pressure and low-level lead exposure was weak with effect sizes for a doubling of the blood lead concentration of 1 mm Hg systolic and 0.6 mm Hg diastolic.[12] A more recent meta-analysis conducted by Navas-Acien and colleagues found statistically significant associations between blood pressure and bone lead but not consistent among the different measures of bone lead.[13] These researchers, summarized data from five cross-sectional studies. All studies measured lead levels in tibia bone and three studies measured lead levels also in patella. For a 10 μg/g increase in tibia lead, the cross-sectional pooled estimates for increases in blood pressure were 0.26 mm Hg systolic (CI, 0.02 to 0.50) and 0.02 mm Hg diastolic (CI, –0.15 to 0.19). For a 10 μg/g increase in patella lead, the pooled odds ratio for hypertension was 1.04 (CI, 0.96 to 1.12). All studies included in Navas-Acien's meta-analysis also measured blood lead. For a 5 μg/dL increment in blood lead, the pooled estimate for an increase in blood pressure was 1.53 mm Hg systolic (CI, –0.19 to 3.25) and 1.19 mm Hg diastolic (CI, –0.69 to 3.08). Navas-Acien also summarized three prospective studies,

but the pooled statistics did not show any association between change in blood pressure or incidence of hypertension with the baseline measures of lead exposure.

Prospective studies in populations or workers

To our knowledge, prospective studies in populations[14-16] or workers[17,18] did not show a consistent relation between change in blood pressure or incidence of hypertension and the baseline biomarkers of lead exposure, either the blood lead concentration[14-18] or bone lead.[14,17,18] We studied a random population sample of 728 people in 1985–1989 (participation rate, 78%) and re-examined the participants in 1991–1995 (81%).[16] At baseline and follow-up, we measured blood pressure by conventional sphygmomanometry (average of 15 readings in total) and at follow-up also by 24-h ambulatory monitoring. Exposure was estimated from lead and zinc protoporphyrin in blood.[16] Blood lead averaged 8.7 µg/dL at baseline and over 5.2 years of follow-up (median) dropped by 2.9 µg/dL (32% decrease). Over the follow-up period no consistent associations emerged between the changes in the conventionally measured blood pressure and in the biomarkers of lead exposure. In addition, baseline blood lead and zinc protoporphyrin did not predict the development of hypertension in 47 patients; the risk ratio for doubling of the initial blood lead was 1.2 (CI, 0.7 to 2.0). Similarly, the 24-h blood pressure at follow-up did not show a consistent relation with the biomarkers of exposure at baseline or at follow-up.

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Table S1. Unadjusted Associations of Systolic and Diastolic Blood Pressure with Blood Lead

Strata by Ethnicity and Sex	Systolic Blood Pressure (mm Hg)			Diastolic Blood Pressure (mm Hg)		
	Effect Size (95% CI)	*r2*, %	*P*	Effect Size (95% CI)	*r2*, %	*P*
Women						
Black (*n*=1346)	6.40 (5.23 to 7.56)	7.93	<0.0001	0.86 (0.15 to 1.58)	0.42	0.018
Hispanic (*n*=1233)	4.99 (3.75 to 6.24)	4.77	<0.0001	0.79 (0.14 to 1.45)	0.45	0.018
White (*n*=3620)	6.99 (6.26 to 7.72)	8.92	<0.0001	0.08 (–0.34 to 0.51)	>0.01	0.69
All women (*n*=6199)	6.50 (5.95 to 7.05)	7.91	<0.0001	0.49 (0.17 to 0.81)	0.14	0.0028
Men						
Black (*n*=1346)	4.38 (3.41 to 5.34)	5.56	<0.0001	1.32 (0.59 to 2.05)	0.93	0.0004
Hispanic (*n*=1374)	2.18 (1.25 to 3.12)	1.50	<0.0001	0.13 (–0.50 to 0.76)	0.01	0.69
White (*n*=3806)	3.40 (2.79 to 4.00)	3.05	<0.0001	–0.22 (–0.65 to 0.22)	0.02	0.33
All men (*n*=6526)	3.31 (2.86 to 3.76)	3.08	<0.0001	0.22 (–0.10 to 0.55)	0.03	0.17
All participants (*n*=12,725)	4.80 (4.46 to 5.14)	5.64	<0.0001	0.67 (0.45 to 0.89)	0.28	<0.0001

Effect sizes (95% confidence interval [CI]) express the change in blood pressure associated with a doubling of the blood lead concentration.

Table S2. Unadjusted Associations of Pulse Pressure and Mean Arterial Pressure with Blood Lead

Strata by Ethnicity and Sex	Pulse Pressure (mm Hg)			Mean Arterial Pressure (mm Hg)		
	Effect Size (95% CI)	*r2*, %	*P*	Effect Size (95% CI)	*r2*, %	*P*
Women						
Black (*n*=1346)	5.52 (4.43 to 6.61)	6.86	<0.0001	2.70 (1.98 to 3.43)	3.80	<0.0001
Hispanic (*n*=1233)	4.20 (3.04 to 5.36)	3.95	<0.0001	2.19 (1.48 to 2.91)	2.87	<0.0001
White (*n*=3620)	6.91 (6.17 to 7.64)	8.51	<0.0001	2.39 (1.97 to 2.81)	3.33	<0.0001
All women (*n*=6199)	6.01 (5.47 to 6.55)	7.12	<0.0001	2.49 (2.17 to 2.81)	3.54	<0.0001
Men						
Black (*n*=1346)	3.06 (2.14 to 3.98)	3.06	<0.0001	2.34 (1.65 to 3.04)	3.18	<0.0001
Hispanic (*n*=1374)	2.05 (1.14 to 2.96)	1.41	<0.0001	0.81 (0.20 to 1.43)	0.49	0.0095
White (*n*=3806)	3.61 (2.99 to 4.23)	3.31	<0.0001	0.99 (0.58 to 1.39)	0.59	<0.0001
All men (*n*=6526)	3.09 (2.64 to 3.53)	2.72	<0.0001	1.25 (0.95 to 1.56)	0.99	<0.0001
All participants (*n*=12,725)	4.13 (3.79 to 4.47)	4.35	<0.0001	2.04 (1.83 to 2.26)	2.69	<0.0001

Effect sizes (95% confidence interval [CI]) express the change in blood pressure associated with a doubling of the blood lead concentration.

Table S3. Unadjusted Associations between Hypertension and Blood Lead

Strata by Ethnicity and Sex	Odds Ratio (95% CI)	*P*
Women		
Black (*n*=1346)	2.14 (1.87 to 2.46)	<0.0001
Hispanic (*n*=1233)	1.51 (1.32 to 1.73)	<0.0001
White (*n*=3620)	2.17 (1.99 to 2.37)	<0.0001
All women (*n*=6199)	2.02 (1.89 to 2.15)	<0.0001
Men		
Black (*n*=1346)	1.63 (1.44 to 1.85)	<0.0001
Hispanic (*n*=1374)	1.10 (0.98 to 1.25)	0.12
White (*n*=3806)	1.53 (1.41 to 1.65)	<0.0001
All men (*n*=6526)	1.41 (1.33 to 1.49)	<0.0001
All participants (*n*=12,725)	1.58 (1.52 to 1.65)	<0.0001

Effect sizes are odds ratios (95% confidence interval [CI]) associated with a doubling of the blood lead concentration.

Table S4. Correlates of Pulse Pressure and Mean Arterial Pressure

Covariables	Pulse Pressure (mm Hg)			Mean Arterial Pressure (mm Hg)		
	Effect size (95% CI)	*r2* (%)	*P*	Effect size (95% CI)	*r2* (%)	*P*
Black *vs.* white (1,0)	1.86 (1.17 to 2.55)	0.90	<0.0001	2.75 (2.25 to 3.36)	1.44	<0.0001
Hispanic *vs.* white (1,0)	3.30 (2.60 to 4.00)		<0.0001	–0.15 (–0.66 to 0.36)		0.56
Female sex (1,0)	…	…	…	–0.35 (–0.81 to 0.12)	0.01	0.15
Age (+18.0 y)	–21.8 (–23.4 to –20.2)	31.7	<0.0001	14.3 (13.1 to 15.5)	8.02	<0.0001
Age^2 (+1875 y^2)	30.5 (28.9 to 32.2)		<0.0001	–12.3 (–13.5 to –11.1)		<0.0001
Body mass index (+6.5 kg/m^2)	0.83 (0.55 to 1.11)	0.14	<0.0001	0.73 (0.52 to 0.93)	0.99	<0.0001
Heart rate (+12.2 beats/minute)	–1.82 (–2.09 to –1.56)	0.57	<0.0001	0.72 (0.52 to 0.91)	0.35	<0.0001
γ-glutamyltransferase (× 2)	1.22 (0.92 to 1.52)	0.31	<0.0001	0.96 (0.74 to 1.18)	0.67	<0.0001
Cotinine (× 2)	0.16 (0.10 to 0.21)	0.14	<0.0001	–0.13 (–0.16 to –0.09)	0.20	<0.0001
Hematocrit (+4.3%)	–1.23 (–1.51 to –0.95)	0.25	<0.0001	1.89 (1.65 to 2.13)	2.50	<0.0001
College graduate (1, 0)	–2.19 (–2.88 to –1.51)	0.39	<0.0001	–1.24 (–1.74 to –0.74)	0.16	<0.0001
Antihypertensive drugs (1,0)	3.87 (3.20 to 4.54)	1.12	<0.0001	1.75 (1.27 to 2.24)	0.37	<0.0001
Dietary sodium-to-potassium ratio (+0.60)	…	…	…	0.34 (0.15 to 0.54)	0.07	0.0006
Serum total calcium (+0.37 mg/dL)	0.62 (0.35 to 0.89)	0.10	<0.0001	0.32 (0.12 to 0.52)	0.06	0.0014
Total explained variance (R^2)		35.6			14.8	

Effect sizes (95% confidence interval [CI]) express the multivariable-adjusted change in blood pressure associated with the explanatory variables, as category, on a linear scale (+ 1-SD), or on a logarithmic scale (doubling). The explanatory variables were selected by a stepwise regression procedure with the *P*-values for variables to enter and stay in the models set at 0.15. The linear and squared terms of age as well as the design variables coding for ethnicity were offered together for entry into the model. An ellipsis indicates that a variable did not enter the model. Variables considered that did not enter in any model were dietary intake of calcium and caffeine, and the poverty index ratio. R^2 and r^2 indicate the variance explained in percent by the whole model or by single or sets of variables.

Table S5. Multivariable Adjusted Association of Pulse Pressure and Mean Arterial Pressure with Blood Lead

Strata by Ethnicity and Sex	Pulse Pressure (mm Hg)			Mean Arterial Pressure (mm Hg)		
	Effect Size (95% CI)	*r2*, %	*P*	Effect Size (95% CI)	*r2*, %	*P*
Women						
Black (*n*=1346)	0.64 (–0.56 to 1.84)	0.05	0.30	0.73 (–0.16 to 1.62)	0.16	0.11
Hispanic (*n*=1233)	0.69 (–0.29 to 1.67)	0.08	0.17	0.10 (–0.62 to 0.82)	>0.00	0.79
White (*n*=3620)	–0.11 (–0.84 to 0.61)	>0.00	0.76	0.69 (0.18 to 1.21)	0.17	0.0081
All women (*n*=6199)	0.15 (–0.37 to 0.67)	>0.00	0.57	0.48 (0.10 to 0.86)	0.09	0.012
Men						
Black (*n*=1346)	0.81 (–0.27 to 1.88)	0.13	0.14	1.08 (0.26 to 1.90)	0.42	0.010
Hispanic (*n*=1374)	0.98 (0.14 to 1.82)	0.28	0.023	0.30 (–0.30 to 0.89)	0.06	0.33
White (*n*=3806)	–0.06 (–0.68 to 0.57)	>0.00	0.86	0.68 (0.23 to 1.14)	0.20	0.0035
All men (*n*=6526)	0.32 (–0.13 to 0.77)	0.02	0.16	0.57 (0.24 to 0.91)	0.15	0.0007
All participants (*n*=12,725)	0.33 (–0.02 to 0.67)	0.02	0.063	0.54 (0.29 to 0.79)	0.12	<0.0001

Effect sizes (95% confidence interval [CI]) express the multivariable-adjusted change in blood pressure associated with a doubling of the blood lead concentration. Estimates were adjusted for ethnicity and/or sex (as appropriate), the linear and squared terms of age, body mass index, heart rate, hematocrit, serum total calcium, γ-glutamyltransferase and cotinine, the dietary sodium-to-potassium intake ratio, college education, and antihypertensive drug treatment.

Table S6. Adjusted Associations of Systolic and Diastolic Pressure with Blood Lead Considering Additional Covariables

Strata by Ethnicity and Sex	Systolic Blood Pressure (mm Hg)			Diastolic Blood Pressure (mm Hg)		
	Effect Size (95% CI)	r^2, %	*P*	Effect Size (95% CI)	r^2, %	*P*
Women						
Black (*n*=1346)	1.31 (–0.07 to 2.69)	0.19	0.062	0.47 (–0.39 to 1.33)	0.07	0.29
Hispanic (*n*=1233)	0.48 (–0.65 to 1.62)	0.03	0.41	–0.28 (–0.97 to 0.40)	0.05	0.41
White (*n*=3620)	0.77 (–0.02 to 1.57)	0.06	0.057	0.66 (0.16 to 1.17)	0.15	0.010
All women (*n*=6199)	0.69 (0.10 to 1.28)	0.06	0.021	0.33 (–0.03 to 0.70)	0.04	0.075
Men						
Black (*n*=1346)	1.60 (0.44 to 2.77)	0.45	0.0071	0.69 (–0.17 to 1.54)	0.15	0.11
Hispanic (*n*=1374)	0.94 (0.03 to 1.85)	0.23	0.042	–0.23 (–0.85 to 0.39)	0.03	0.46
White (*n*=3806)	0.59 (–0.10 to 1.27)	0.06	0.092	0.48 (0.01 to 0.95)	0.08	0.047
All men (*n*=6526)	0.75 (0.25 to 1.24)	0.11	0.0029	0.27 (–0.07 to 0.61)	0.03	0.12
All participants (*n*=12,725)	0.78 (0.40 to 1.16)	0.09	<0.0001	0.28 (0.03 to 0.53)	0.03	0.0029

Effect sizes (95% confidence interval [CI]) express the multivariable-adjusted change in blood pressure associated with a doubling of the blood lead concentration. Estimates were adjusted for ethnicity and/or sex (as appropriate), the linear and squared terms of age, body mass index, heart rate, hematocrit, serum creatinine, total calcium, γ-glutamyltransferase and cotinine, the dietary sodium-to-potassium intake ratio, college education, diabetes mellitus, and antihypertensive drug treatment.

Table S7. Adjusted Associations of Pulse Pressure and Mean Arterial Pressure with Blood Lead Considering Additional Covariables

Strata by Ethnicity and Sex	Pulse Pressure (mm Hg)			Mean Arterial Pressure (mm Hg)		
	Effect Size (95% CI)	r^2, %	*P*	Effect Size (95% CI)	r^2, %	*P*
Women						
Black (*n*=1346)	0.82 (–0.39 to 2.03)	0.09	0.19	0.74 (–0.15 to 1.63)	0.17	0.10
Hispanic (*n*=1233)	0.77 (–0.22 to 1.75)	0.10	0.13	–0.03 (–0.75 to 0.70)	>0.00	0.94
White (*n*=3620)	0.12 (–0.61 to 0.84)	<0.00	0.75	0.70 (0.19 to 1.22)	0.17	0.0078
All women (*n*=6199)	0.36 (–0.17 to 0.88)	0.02	0.18	0.45 (0.073 to 0.83)	0.07	0.019
Men						
Black (*n*=1346)	0.92 (–0.16 to 2.01)	0.17	0.094	1.00 (0.17 to 1.82)	0.35	0.018
Hispanic (*n*=1374)	1.17 (0.32 to 2.02)	0.39	0.0070	0.16 (–0.45 to 0.77)	>0.00	0.60
White (*n*=3806)	0.11 (–0.52 to 0.74)	<0.00	0.74	0.51 (0.05 to 0.98)	0.11	0.030
All men (*n*=6526)	0.48 (0.02 to 0.93)	0.05	0.040	0.43 (0.09 to 0.77)	0.08	0.012
All participants (*n*=12,725)	0.50 (0.15 to 0.85)	0.04	0.0046	0.44 (0.19 to 0.70)	0.08	0.0005

Effect sizes (95% confidence interval [CI]) express the multivariable-adjusted change in blood pressure associated with a doubling of the blood lead concentration. Estimates were adjusted for ethnicity and/or sex (as appropriate), the linear and squared terms of age, body mass index, heart rate, hematocrit, serum creatinine, total calcium, γ-glutamyltransferase and cotinine, the dietary sodium-to-potassium intake ratio, college education, diabetes mellitus, and antihypertensive drug treatment.

Table S8. Adjusted Association between Hypertension and Blood Lead Considering Additional Covariables

Strata by Ethnicity and Sex	**Odds Ratio (95% CI)**	***P***
Women		
Black (*n*=1346)	0.82 (0.67 to 1.01)	0.063
Hispanic (*n*=1233)	0.91 (0. 75 to 1.11)	0.36
White (*n*=3620)	1.09 (0.96 to 1.24)	0.20
All women (*n*=6199)	0.98 (0.89 to 1.07)	0.64
Men		
Black (*n*=1346)	0.99 (0.82 to 1.19)	0.93
Hispanic (*n*=1374)	0.90 (0.75 to 1.06)	0.21
White (*n*=3806)	1.00 (0.90 to 1.12)	0.94
All men (*n*=6526)	0.97 (0.89 to 1.05)	0.39
All participants (*n*=12,725)	0.98 (0.92 to 1.04)	0.51

Effect sizes (95% confidence interval [CI]) express the multivariable-adjusted risk of having hypertension associated with a doubling of the blood lead concentration. Odds ratios were adjusted for ethnicity and/or sex (as appropriate), the linear and squared terms of age, body mass index, heart rate, hematocrit, serum creatinine, total calcium, γ-glutamyltransferase and cotinine, college education, the dietary sodium-to-potassium intake ratio, and diabetes mellitus.

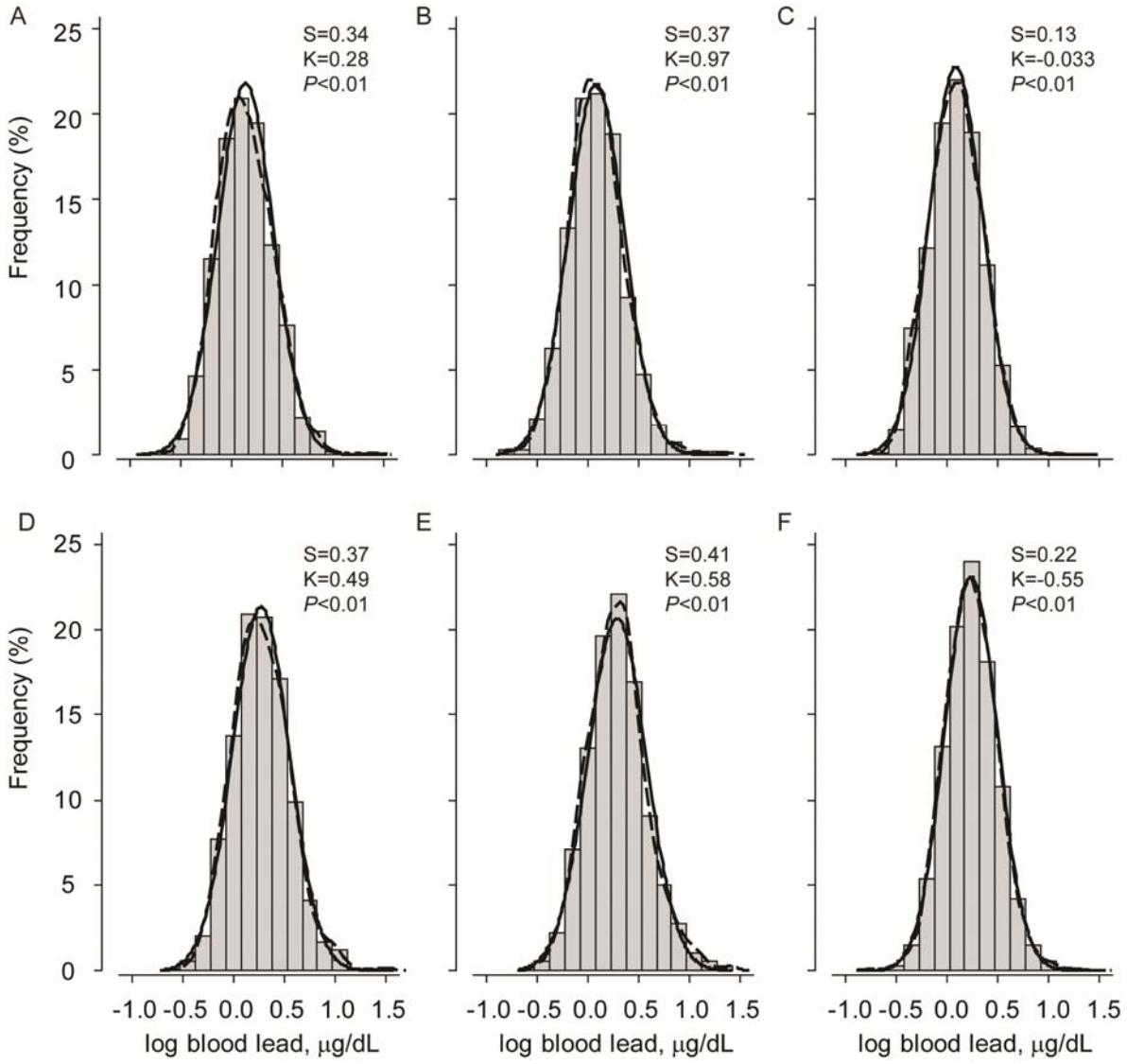

Figure S1.

Distributions of the log blood lead concentration by ethnicity (Blacks, A and D; Hispanics, B and E; and Whites, C and F) and sex (women, A, B, and C; men D, E, and F). S and K are the coefficients of skewness and kurtosis, respectively. The dotted line is the fitted normal distribution; the full line is the fitted Kernel distribution; and the *P*-value calculated by Kolmogorov-Smirnov test are for departure from normality.

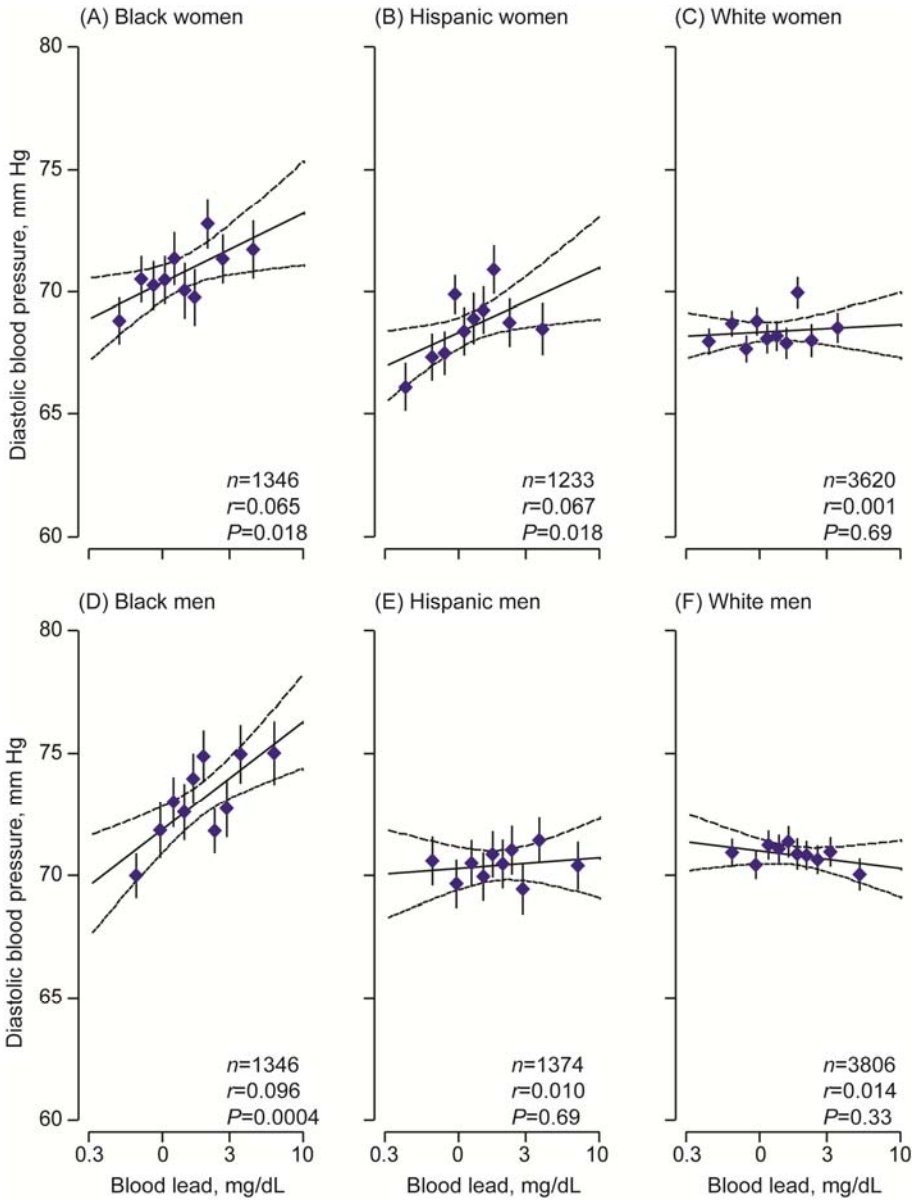

Figure S2.

Unadjusted associations between diastolic blood pressure and blood lead by 6 ethnicity-sex strata. The regression line with 95% confidence interval was computed using the individual subjects in each stratum. The dots plotted over the regression line represent the means of diastolic blood pressure and lead in each decile of the ethnicity- and sex-specific distributions. Vertical bars denote the standard error of diastolic blood pressure. The Figure illustrates the adequacy of the linear model.