Blood Lead and Blood Pressure

Relationship in the Adolescent and Adult US Population

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• **Heavy lead exposure has been connected to cardiovascular disease, but modest exposures encountered in the general environment have not been associated previously with disease risk. The relationship between blood lead levels and blood pressures was examined using data from the second National Health and Nutrition Examination Survey. A direct relationship was found between blood lead levels and systolic and diastolic pressures for men and women and for white and black persons aged 12 to 74 years. Blood lead levels were significantly higher in younger men and women (aged 21 to 55 years) with high blood pressure, but not in older men or women (aged 56 to 74 years). In multiple regression analyses, the relationship of blood lead to blood pressure was independent of other variables for men, but not for women. Dietary calcium and serum zinc levels were inversely related to blood pressure.**

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INTENSE and prolonged lead exposure has a long historical association with toxic effects to multiple organ systems, including the cardiovascular system.[1,2] Early observations of cardiovascular toxic effects disclosed an increased incidence of stroke or renal impairment following heavy industrial exposures, and hypertension has been found in association with toxic reactions to lead following consumption of lead-containing moonshine whiskey.[3] Recently, interest has shifted to possible harmful effects of lead at lower levels of exposure that are commonly found in the general population. Potential effects on childhood intellectual development and on adult blood pressure have been described in populations encountering common environmental sources.[4,5] The second National Health and Nutrition Examination Survey (NHANES-II) examined a representative sample of the US population and found that blood lead levels were related to ambient environmental exposures.[6,7] The levels for many children in this survey were above levels potentially associated with health effects, although the threshold level for toxic effects remains controversial. In adolescents and adults, toxic effects of low-level exposure to lead have received less attention, but several studies have indicated that commonly encountered lead exposure may be directly related to elevated blood pressure.[5,8] These studies have demonstrated a direct relationship between blood pressure and relatively low levels of lead exposure.[5,8]

The relationship between lead and blood pressure has additional interest because it may clarify recent observations about the association between calcium intake and blood pressure.[9-11] Lower dietary calcium intake is associated with higher blood pressures. Lead and calcium follow similar metabolic pathways, and decreased calcium intake could aggrevate the toxic effects of lead exposure.[12,13] Other nutritional factors and trace metals have been shown to aggrevate or ameliorate toxic effects of lead. To examine possible relationships between blood lead and blood pressure in a representative US population, we analyzed data from the adolescent and adult components of NHANES-II.[14] This survey includes extensive nutritional and trace metal data that permit examination of the blood lead and blood pressure associations as well as interactions among environmental variables. A direct relationship is documented between blood lead and blood pressure at relatively low blood lead levels in these analyses.

POPULATION AND METHODS

The NHANES-II was conducted from 1976 to 1980 on a representative sample of the civilian, noninstitutionalized US population aged 6 months to 74 years. A probability sample of 27,801 persons was selected, and 20,322 were examined (73% response rate). The complex sampling

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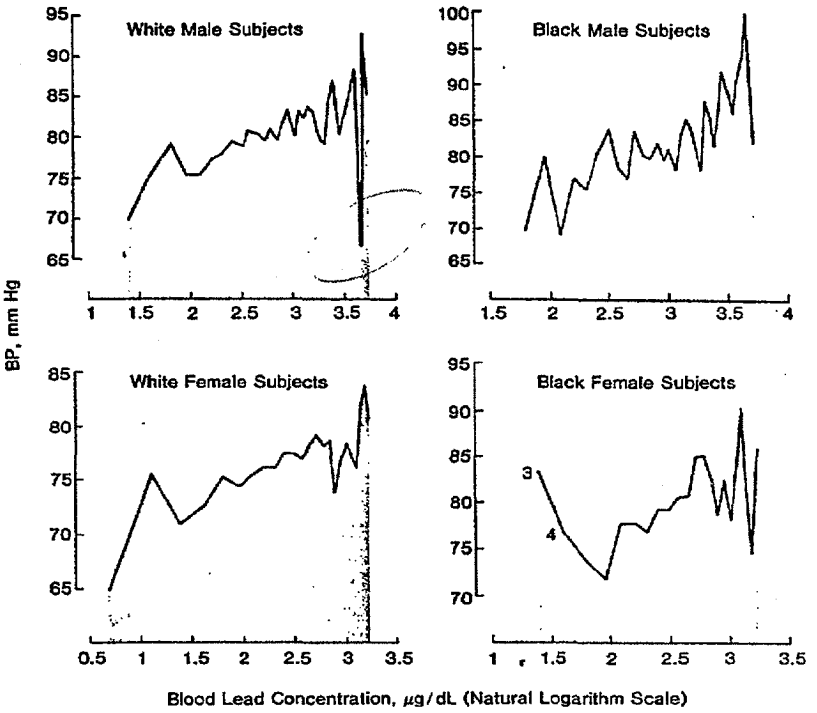
design and details of the examination procedures, laboratory performance, and quality control are contained in several reports.[14,15] Examinations were performed in mobile examination centers, and the medical evaluation included medical history, physical examination, anthropometric measurements, dietary interview (24-hour dietary recall and food frequency), laboratory tests, ECGs, and chest roentgenograms. A manual of operations, special interview and examination protocols, and specifically trained interviewers and examiners were utilized to maintain structured and standardized conduct of the survey at all sites. Dietary intakes were determined by 24-hour dietary recall and by questionnaires about frequency of consumption of foods. The nutrient intake from the 24-hour recall was quantified for each person using a current nutrient data bank. The frequency of consumption of food groups was scaled to permit quantification of customary food consumption for the six months preceding the examination.

Three blood pressures were recorded for each examinee: with the patient seated early in the examination, supine midway through the examination, and again seated near the end of the examination. The American Heart Association recommendations on blood pressure recording were followed and an appropriate sized cuff selected. The first- and fifth-phase Korotkoff sounds were taken as systolic and diastolic pressures, respectively. The second seated blood pressure was used in these analyses, but analyses using the first pressure with the patient seated or a mean of both pressures with the patient seated afforded similar results. Height and weight were measured in a standardized manner, and skin-fold thickness was measured in the triceps and subscapular areas using Lange skin-fold calipers.

Blood for hematologic and nutritional analysis was obtained by venipuncture. After preparation, these samples were shipped to the Clinical Chemistry Division, Center for Environmental Health, Centers for Disease Control, Atlanta, and analyzed.[16] Blood lead was analyzed by atomic absorption spectrometry on odd-numbered samples from examinees aged 12 to 74 years.[16,17] Specimens were analyzed in duplicate, and an extensive quality-control system was used to ensure accurate assessment without laboratory drift.[8] Serum zinc and serum copper were analyzed by atomic absorption spectrometry.[18,19]

The analysis of data from complex sample designs such as used in the NHANES-II requires special statistical techniques if the findings are to be projected as representative of the US population.[20] All statistical analyses were performed using these analytic approaches, and, consequently, the results can be extrapolated to the general population during the 1976-1980 period.[20] The analytic strategies and the computer software used to implement these weighted analyses are described in detail elsewhere.[20,21] Because of skewed distributions, blood lead levels were transformed to the natural logarithm for correlational analysis.



Relationship between diastolic blood pressure and natural logarithm of blood lead concentration for four race-sex groups aged 12 to 74 years during period 1976 to 1980. Sample sizes are limited at extremes of distributions and variability is increased. For black women, parentheses indicate that these points comprise only three or four persons.

The relationships between blood pressure and other variables were examined in two ways. Men and women were stratified into normotensive and hypertensive categories and mean values for relevant variables contrasted across the categories. Diastolic high BP was defined as 90 mm Hg or above for younger persons (aged 24 to 55 years) and for older persons (aged 56 to 74 years). Isolated systolic high BP was defined as systolic pressure of 160 mm Hg or greater and diastolic pressure less than 90 mm Hg. This condition was found primarily for those aged 56 to 74 years. Differences in mean values for these variables between the blood pressure subgroups were tested using an adjusted t statistic.[20]

Simple correlations between blood pressure and blood lead were determined, and multiple linear regression models were used to explore and clarify the numerous joint relationships among selected variables and blood pressure. For example, blood pressure had numerous significant relationships to age, weight, nutrient intake (including dietary calcium), and trace metals. These joint effects on blood pressure were clarified by fitting the multiple linear regression models in a stepwise manner using systolic and diastolic pressures as the dependent variables. This technique selects initially the independent or predictor variable that explains the greatest variance in the dependent variable (systolic or diastolic pressure) and selects additional explanatory variables only if they make significant independent contributions after adjusting for the effect of previously selected variables. Thirty-four variables were identified as having significant univariate correlations with blood pressure and were entered into this stepwise procedure. Separate predictive models were developed for men and women. The final predictive models contained only variables making statistically significant ($P<.05$) contributions after utilizing techniques to adjust for the complex survey design and sample. To test for the effect of pharmacologic therapy, predictive models were developed for the subsample of persons who were not receiving

Table 1.—Mean (±SE) Body Mass Index, Calcium Food Intake, and Levels of Blood Lead, Serum Zinc, and Hemoglobin by Blood Pressure Category for Men and Women, US Population, 1976 to 1980

Variables by Subgroup	Ages 21-55 yr: Normal BP (<90 mm Hg)	Ages 21-55 yr: Diastolic High BP (≥90 mm Hg)	Ages 56-74 yr: Normal BP (<160 and <90 mm Hg)	Ages 56-74 yr: Diastolic High BP (≥90 mm Hg)	Ages 56-74 yr: Systolic High BP (≥160 and <90 mm Hg)
Men					
Sample size	1,043	475	660	353	38
Blood lead, μg/dL	16.9*(±0.33)	17.9*(±0.49)	16.4 (±0.28)	16.9 (±0.50)	16.5 (±1.37)
Body mass index, kg/sq m	24.7 (±0.13)	27.4*(±0.26)	25.4 (±0.18)	27.1*(±0.23)	24.9 (±0.73)
Serum zinc, μg/dL	92.0 (±0.76)	91.6 (±0.90)	88.3 (±0.96)	86.9 (±0.99)	81.1*(±3.11)
Calcium foods†	12.9 (±0.33)	11.1*(±0.44)	11.4 (±0.41)	10.5 (±0.39)	13.7 (±1.93)
Hemoglobin, g/dL	15.1 (±0.05)	15.5 (±0.08)	14.9 (±0.08)	15.0 (±0.07)	14.4*(±0.18)
Women					
Sample size	1,316	263	769	320	68
Blood lead, μg/dL	11.5 (±0.26)	12.3*(±0.38)	12.9 (±0.34)	12.9 (±0.31)	13.1 (±1.10)
Body mass index, kg/sq m	23.8 (±0.19)	28.6*(±0.43)	25.4 (±0.21)	29.2*(±0.36)	25.8 (±1.13)
Serum zinc, μg/dL	84.1 (±0.55)	83.0 (±1.07)	85.0 (±0.61)	82.5*(±0.97)	82.8 (±1.78)
Calcium foods	11.2 (±0.40)	10.0*(±0.53)	11.5 (±0.42)	10.2*(±0.51)	11.0 (±1.17)
Hemoglobin, g/dL	13.3 (±0.05)	13.4 (±0.11)	13.6 (±0.06)	13.8 (±0.09)	13.3 (±0.24)

*Denotes statistical significance at $P \leq .05$.
†Scaled frequency of consumption.

antihypertensive therapy and the models compared with the entire group including those receiving therapy. No important differences were identified, so the reported results comprise all individuals having blood lead determinations.

RESULTS

Blood lead levels were directly related to systolic and diastolic blood pressures for men and women aged 12 to 74 years. The relationship between the natural logarithm of blood lead and diastolic pressures is illustrated for the four race-sex groups in the Figure. The correlation coefficients for white and black women were .11 and .22 ($P<.0005$), respectively, and for white and black men were .16 and .11 ($P<.001$), respectively. The relationship was essentially linear, but the means were less stable at either end of the distribution of lead values because of small sample sizes, particularly for the black subgroups. Because of the observed secular trend downward in blood lead levels during the 1976-1980 survey period,[1] comparisons were made for each of the four years in the survey. A similar linear relationship was found for each year of the survey.

Men and women were stratified by blood pressure status and separated into two age groups (Table 1). Blood lead levels were significantly higher in younger men and women (aged 21 to 55 years) with high diastolic pressure than in those with normal blood pressure ($P<.05$). However, in older persons (aged 56 to 74 years), blood lead levels were not significantly different for any of the blood pressure categories and there were no important trends. Serum zinc levels were significantly lower for older hypertensive women and for men with isolated systolic hypertension. For younger persons, serum zinc levels tended to be lower in those with hypertension, but this was not statistically significant. Dietary calcium intake (calcium foods) was significantly lower in younger hypertensive men and women, but in the older group was significantly lower only for hypertensive women. These findings regarding calcium intake and blood pressure are similar to those from the earlier NHANES-I survey.[2] Men and women in both age ranges had significantly greater body mass index (weight/height^2) with diastolic blood pressure elevation, but no differences were found for systolic high blood pressure. Blood lead levels and serum zinc levels were higher for men than for women, except for serum zinc among those classified as having isolated systolic high blood pressure, where there was no significant difference between men and women.

Predictive models for systolic and diastolic blood pressures are presented for men (Table 2) and for women (Table 3). The variance explained by the model (r^2) and the sample size (n) are indicated in the first and second lines of each table. Each of these standardized regression coefficients is statistically significant ($P<.05$) when incorporating both the weights and the design effects into the final model. Age and body mass

Table 2.—Standardized Coefficients for Multiple Regression Models of Systolic and Diastolic Pressures in Men

Variable	Systolic	Diastolic
r^2	.236	.274
n	2,823	2,818
Age	.230	.176
Age^2	.100	−.109
Body mass index (weight/height^2)	.330	.328
Age (blacks)	.042	.040
Race	. . .	.070
Blood lead (ln scale*)	.061	.049
Hemoglobin	.074	.114
Serum zinc	−.046	−.038

*Blood lead analyzed on natural logarithm scale.

Table 3.—Standardized Coefficients for Multiple Regression Models of Systolic and Diastolic Pressures in Women

Variable	Systolic	Diastolic
r^2	.363	.269
n	2,905	2,897
Age	.430	.212
Age^2	.184	−.039
Body mass index (weight/height^2)	.290	.356
Serum zinc	−.058	−.052
RBCs	.060	.105
Dietary calcium	−.039	−.048
Alcohol (oz/wk)	. . .	.054

index were significant and independent predictors of blood pressure in NHANES-II, as was previously found in NHANES-I, conducted from 1971 to 1975.[9] An age-squared term was selected because the relationship between blood pressure and age is curvilinear across this wide age range. For men older than 55 years of age, diastolic pressure has a more rapid increase in slope than for older women. Blood pressure increases more rapidly with age in black persons, primarily men, and the race variables in Table 2 quantify this relationship. For men, blood lead had a significant relationship to systolic and diastolic pressure that is independent of the relationships between other variables and blood pressure. Although the simple linear relationship between blood lead and blood pressure was statistically significant for women, blood lead was not independently related to blood pressure after adjusting for the joint effects of the other predictors in the model (Table 3). Serum zinc was inversely related to blood pressure for both men and women. Dietary calcium intake was inversely related in women, but not in men. Alcohol intake was directly related to diastolic pressure in women. Red blood cell count or hemoglobin level was directly related to blood pressure in women and men, respectively. The predictive models explained more variance in blood pressure (r^2 of .23 to .36) than did similar models from the NHANES-I that did not include trace metal measurements.[9]

COMMENT

Lead is ubiquitous in the human environment and has no known metabolic utility but does have a potential for toxic health effects. In this survey of the US population conducted from 1976 to 1980, there was a direct and linear relationship between blood lead and blood pressure. This association was statistically significant for systolic and diastolic pressures, and the effect was found at blood lead levels of less than 30 μg/dL, which is the current "toxic" definition for occupational exposure.[21] This direct relationship was observed in men and women and in both races, despite differing levels of blood lead and blood pressure among the race-sex groups. In the United States, blood lead levels are relatively higher in blacks than whites and higher in men than women, and, interestingly, these same relative race-sex rankings apply to blood pressures for younger persons. There is no ready explanation for the race-sex differences in blood lead levels, although heavier occupational exposures, urban environment, and perhaps different metabolic handling have been cited.[22-25] The relationship of blood lead to blood pressure has clinical relevance. Younger men and women (aged 24 to 55 years) with diastolic high blood pressure had significantly higher blood lead levels than those with normal pressures (Table 1). However, there were no significant differences in blood lead levels in older men and women (aged 56 to 74 years) with diastolic high blood pressure or isolated systolic high blood pressure. In general, previous reports of an association between body lead and hypertension have focused on heavily exposed individuals with high (>60 μg/dL) blood lead levels. An important exception is the report of Beevers et al,[5] who studied individuals living in an area of Scotland with relatively high levels of lead in the water supply. They found that hypertensive men had significantly higher blood lead levels (27 μg/dL) than normotensive men (24 μg/dL), although the ranges for both groups were at levels customarily considered "safe." Therefore, in this US survey and in the Scottish study, significant relationships to blood pressure were found at lead levels previously considered "nontoxic."

Many environmental factors can influence blood pressure, and initial analyses of NHANES-II indicated that more than 30 variables had statistically significant associations, many representing overlapping or confounding relationships. To determine whether the lead relationship to blood pressure was an independent effect, multiple regression models were developed. This analytic approach adjusts for the contribution of each predictive variable as it is selected and adds new variables only if they contribute independently to the prediction. For example, age and body mass were both strongly related to blood pressure, and this relationship was partially confounded by increasing weight at older ages. Moreover, blood lead levels increase with age, as does blood pressure. The multiple regression analysis permits separation of the unique effects of age, weight, and blood lead while adjusting for the confounding effects of generally parallel trends in age, weight, blood lead levels, and blood pressure. Using this analytic technique, blood lead was found to contribute independently to the prediction of systolic and diastolic pressure in men, even after adjusting for the contributions of more than 30 other variables (Table 2). Dietary calcium was among the variables having a blood pressure relationship when considered alone, and this is illustrated by the significantly lower dietary calcium intake in hypertensive persons (Table 1). However, when lead was included in the model, dietary calcium was not selected in the prediction of male blood pressure but was selected for female blood pressure, and blood lead was not. Although blood lead levels were lower on average for women than men at every age and for both races, this probably does not explain the lack of an independent lead effect in women. Human and animal studies have indicated that at comparable levels of exposure, blood lead levels are lower for females than males and the toxic manifestations are less.[5,23,24] In the study by Beevers and colleagues,[5] significantly higher blood lead levels were found for men with hypertension than for normotensive men. However, women with hypertension did not have significantly higher blood lead levels than normotensive women.

Nutrients and trace metals, especially cations, can ameliorate or aggrevate toxic effects of lead. Calcium and zinc have metabolic and physiological effects that compete with lead, and decreased intake of calcium, in particular, can aggrevate the toxic effects of lead. Diets deficient in calcium increase lead absorption and decrease excretion. In recognition of this effect, it was common to provide workers in the lead industry with free milk to prevent occupational toxic effects of lead.[25] In this survey, the earlier NHANES-I, and other population surveys, low calcium intake has been associated with higher

blood pressures.[9-11] The survey finding that lower dietary calcium and higher blood lead levels are associated with higher blood pressures is compatible with the known metabolic interactions among these metallic cations. Zinc is similar to calcium in its tissue metabolic interactions with lead,[25] and the multivariate model suggests that zinc has an effect on blood pressure that opposes the effect of lead. However, lower zinc levels per se are not associated with hypertension (Table 1).

No causal inferences should be drawn from this cross-sectional survey about the blood pressure effects of lead, calcium, and zinc, although these observations from the general population are consistent with extensive animal studies of lead toxic effects and trace metal interactions. Animal studies have investigated the ability of various levels of lead exposure to alter blood pressure and explored mechanisms that linked lead exposure to elevated blood pressure. Recent animal studies have focused on relatively low levels of exposure and have found that blood pressure can be increased at blood lead levels of 40 μg/dL.[26] The increased blood pressures developing at these low lead exposures have been characterized by increased plasma renin and altered vascular reactivity to α-adrenergic stimulation.[24,26] There is no direct evidence that these mechanisms are important in humans, although a case report indicates renin suppression with hypertension in chronic lead intoxication, and these changes were attributed to lead deposition in the kidney.[3] Batuman et al[8] found increased tissue lead that could be mobilized by chelation in hypertensive persons. They suggested that renal toxic reactions were responsible for the hypertension. The patient populations studied by these workers had greater lead exposure than would be found in the general population, and the proposed mechanisms of renal damage or renin alteration may not be directly referable.

Multiple environmental sources exist for human exposure to lead. Occupational exposure, ambient environment, and consumption of water from lead piping have been linked to elevated blood lead levels.[2,5,27] Analyses of data from this survey indicate that in the United States, a major alterable source for the general population is atmospheric contamination with alkyllead from gasoline additives.[6] The 37% decline in blood lead levels during the years of this national survey, 1976 to 1980, and the high correlation (0.95) between lead production and blood lead are compatible with the conclusion that this represents a major environmental source.[6] During this period, lead additives to gasoline were reduced, as was total consumption of automotive gasoline, and blood lead levels declined in the general population. Water, principally soft water, can contain elevated concentrations of lead apparently released from the piping.[7] However, a recent study in Boston, which has soft water, found no relationship between the lead content of water and blood pressure.[28] Our analyses of the NHANES-II data provide a link between blood lead levels and blood pressure, but the cross-sectional nature of the survey limits inferences of causality.

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