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THE RELATIONSHIP BETWEEN BLOOD LEAD LEVELS AND BLOOD PRESSURE AND ITS CARDIOVASCULAR RISK IMPLICATIONS

JAMES L. PIRKLE,[1] JOEL SCHWARTZ,[2] J. RICHARD LANDIS[3] AND WILLIAM R. HARLAN[4]

Pirkle, J. L. (CDC, Atlanta, GA 30333), J. Schwartz, J. R. Landis and W. R. Harlan. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. *Am J Epidemiol* 1985;121:246–58.

The relationship between blood pressure and blood lead levels in the second National Health and Nutrition Examination Survey (1976–1980) has been examined for white males aged 40–59 years. After adjustment for age, body mass index, nutritional factors, and blood biochemistries in a multiple linear regression model, the relationship of systolic and diastolic blood pressures to blood lead levels was statistically significant ($p < 0.01$). There was no evidence of a threshold blood lead level for this relationship. Although these data alone do not prove a causal relationship between low blood lead levels and blood pressure, the findings are consistent with current epidemiologic and animal studies, indicating that a causal relationship is probable. To examine the potential health risks, the multiple logistic risk factor coefficients from the Pooling Project and Framingham studies were used to predict the impact of the 37% decrease in mean blood lead levels which occurred in adult white males from 1976 to 1980. As a result of this blood lead decrease, the calculations predicted a 4.7% decrease in the incidence of fatal and nonfatal myocardial infarction over 10 years, a 6.7% decrease in the incidence of fatal and nonfatal strokes over 10 years, and a 5.5% decrease in the incidence of death from all causes over 11.5 years. In addition, as a result of this blood lead decrease, the predicted number of white males in this age group with hypertension (diastolic blood pressure ≥90 mmHg) decreased by 17.5%.

blood pressure; cerebrovascular disorders; lead; myocardial infarction

High blood pressure is a major public health problem in the United States. Epidemiologic studies have examined sociodemographic, nutritional, and physiologic correlates of high blood pressure to understand better the causes and associated risk factors for hypertension. National health surveys have been useful in providing a large data base of information on persons selected to be representative of the civilian, noninstitutionalized US population. The National Health and Nutrition Examination Survey I (NHANES I) was conducted from 1971 to 1975 and provided extensive information on blood pressure and a large number of related variables. Several analyses of the NHANES I blood pressure data base have been published (1–4).

The second National Health and Nutrition Examination Survey (NHANES II) was conducted from 1976 to 1980 and measured blood pressure as well as a broad array of pertinent sociodemographic, nutritional, and physiologic factors. Whole blood lead measurements were included in NHANES II, but not in NHANES I. Initial

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Abbreviation: NHANES, National Health and Nutrition Examination Survey.

[1] Center for Environmental Health, Centers for Disease Control, Atlanta, GA 30333. (Reprint requests to Dr. James L. Pirkle.)
[2] Environmental Protection Agency, Washington, DC.
[3] University of Michigan School of Public Health, Ann Arbor, MI.
[4] University of Michigan School of Medicine, Ann Arbor, MI.

multiple regression analyses of the blood pressure data from NHANES II (5) found that lead was significantly associated with systolic and diastolic blood pressures in males 12–74 years of age. Lead remained statistically significant even after adjusting for age, race, body mass index, and the other variables which were significant at the 5 per cent level. In addition, lead and age were partially confounded in such a way that the strength of the relationship between lead and blood pressure may have been underestimated.

The present analysis of the NHANES II blood pressure data had three objectives, of which the first was to examine the relationship of blood lead levels to blood pressure in a restricted subgroup, white males aged 40–59 years. Over this age range, age effects on blood pressure are small, permitting better separation of the effects of lead and age on blood pressure. In addition, confining the analyses to white males obviates the confounding of sex and race effects. The second objective was to estimate conservatively the strength and independence of the association between lead and blood pressure. The third objective was to use the multiple logistic risk factor coefficients from the Pooling Project and Framingham studies to estimate the potential public health implications of the relationship between blood lead and blood pressure. Risk factor coefficients were available specifically for white males aged 40–59 years.

Materials and Methods

Survey description

NHANES II was conducted from February 1976 to February 1980 on a sample selected to be representative of the civilian, noninstitutionalized US population aged six months to 74 years. A total of 20,322 persons were examined. Details of the complex survey design, nonresponse adjustments, the examination procedures, and laboratory measurements have been published (6, 31). Examinations were performed in mobile examination centers which traveled to 64 different sites across the United States. The medical evaluation included medical history, physical examination, anthropometric measurements, dietary interview (24-hour recall and food frequency), laboratory tests, electrocardiograms, and radiographs. 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 questionnaires about frequency of food consumption. The nutrient intake from the 24-hour recall was quantified for each individual using a current nutrient data bank.

Blood samples were analyzed by the Clinical Chemistry Division, Center for Environmental Health, Centers for Disease Control (Atlanta, Georgia). Details of the methodology and quality control for the various analytes are available (7). Blood lead concentrations were determined by atomic absorption spectrophotometry by means of a modified Delves-cup micromethod (8, 9). Cholesterol measurements were made by the George Washington Lipid Research Clinic Laboratory and referenced to the Abell-Kendall method (10).

Blood pressure measurements were made with an appropriate size cuff, following the recommendations of the American Heart Association. The first- and fifth-phase Korotkoff sounds were taken as systolic and diastolic pressures, respectively. Three blood pressures were recorded for each examinee: a seated blood pressure early in the examination, a recumbent blood pressure at the end of the examination, and a second seated blood pressure at the end of the examination. The second seated blood pressure was used in these analyses, but similar results were obtained by analysis of the first seated blood pressure, the recumbent blood pressure, and the mean of the first and second seated blood pressures. Regression analysis indicated that the relationship be-

tween blood pressure and blood lead was not significantly affected by whether or not persons were on hypertensive medication. Therefore, persons on hypertensive medication were included in the analyses.

The Pooling Project and Framingham studies were longitudinal epidemiologic investigations of cardiovascular morbidity and mortality. In these studies, multiple logistic regression analyses were conducted to evaluate risk factors for myocardial infarction (11), stroke (P. Sortie, National Heart, Lung, and Blood Institute, personal communication, 1984), and death from all causes (12). In these logistic analyses, fatal and nonfatal myocardial infarctions were defined by standard electrocardiogram changes and, when available, serum enzyme changes. Sudden death was attributed to fatal infarction when a man who was in apparent good health died within three hours of onset of symptoms with no history of violence or accident causing the fatal outcome. Fatal or nonfatal stroke included hemorrhagic and thrombotic strokes as well as transient ischemic attacks and was defined according to published criteria (13).

Statistical procedures

Multiple linear regression models were used to determine which variables were significantly related to blood pressure. Since the NHANES II data were obtained from a complex, multistage probability sample, final hypothesis testing in the multiple regression analysis needed to incorporate the sampling weights and the complex survey design effects. Special computer programs are available (SURREGR (14, 15), REPERR (16)) which allow the design effects to be incorporated into the variance estimates. SURREGR, which runs in the Statistical Analysis System (SAS) environment, was used in this analysis. Compared with SURREGR, standard weighted multiple linear regression yields the same estimates for regression coefficients, but in our experience generally (although not always) gives a lower estimate of the standard error of the coefficient. Thus, standard weighted multiple linear regression usually finds more variables to be statistically significant than after design effects are incorporated using SURREGR.

The general procedure for variable selection was as follows. First, weighted stepwise multiple linear regression was used to determine which variables were significantly related ($p < 0.05$) to blood pressure (SAS; Proc STEPWISE; Stepwise and MAXR options). As noted above, weighted multiple linear regression selects the variables which would be significant after the design effects are incorporated with SURREGR but can select additional variables that would not maintain statistical significance after incorporating the design effects. Therefore, the set of variables chosen by weighted stepwise multiple linear regression was used as a starting variable set for SURREGR. Since SURREGR cannot be implemented in a stepwise fashion, subsequent variable selection was performed by backward elimination using additional runs of SURREGR. This backward elimination step excluded only one variable in the systolic blood pressure analysis and only one variable in the diastolic blood pressure analysis, so the design effects had little influence on final variable selection. Unweighted stepwise multiple linear regression was also used to be sure there were no important differences in the significance of lead between unweighted and weighted analyses.

The natural log of blood lead was more normally distributed and usually more statistically significant than untransformed blood lead. The results reported here are for the natural log of blood lead, but regressions using lead on the untransformed scale gave very similar results. Age was also modeled as a single variable (sine of age) instead of age and age-squared, with no change in results.

The multiple logistic regressions were also performed using programs from SAS. Proc LOGIST was used for the stepwise unweighted multiple
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unweighted multiple logistic regression, and Proc NLIN (nonlinear regression) was used for the weighted logistic regression calculations. Calculations of threshold levels for effects were made using Proc NLIN on segmented regression models (17).

Results

Multiple regression analyses

The first goal of the analysis was to determine if blood lead levels were significantly related to blood pressure in white males aged 40–59 years. The well documented correlates of blood pressure are age, sex, race, and one of the indices of relative height to weight. Body mass index (weight/height^2) was used in this analysis. By limiting our attention to 40- to 59-year-old white males, there was no need to control for race, sex, and, to a large degree, age. Although age was only occasionally significant in the stepwise analysis, both age and age-squared were forced into each multiple regression model to be certain any effect of lead was independent of age over this age range.

The first set of regressions analyzed systolic and diastolic blood pressures for white males 40–59 years of age with a model consisting of age, age-squared, body mass index, and blood lead. These regressions were done to determine whether blood lead levels were significantly associated with systolic and diastolic blood pressures after controlling for age, sex, race, and body mass index, which are well documented correlates of blood pressure. Lead was statistically significant ($p < 0.01$) for both systolic and diastolic blood pressures in all the regressions (unweighted, weighted, and weighted with design effects).

These models were expanded to incorporate additional variables with particular attention directed at the stability and significance of the lead coefficient in the presence of nutritional factors and blood biochemistries. Our objective was not to evaluate the possible associations of nutritional or biochemical measurements with blood pressure, but rather to estimate conservatively the strength and independence of the relationship between blood pressure and blood lead. Therefore, to provide an unusually rigorous test of the independent significance of blood lead, almost all the nutritional and biochemical variables in NHANES II were included in the stepwise regression. In addition, to account for possible curvilinear relationships, squared and natural logarithmic transformations of almost all these variables were also included (see table 1).

Including these additional 87 variables increases the probability of a variable being found statistically significant at the 5 per cent level due to chance alone. This would complicate the interpretation of nutritional and biochemical factors, but including these additional variables only makes it more difficult for lead to maintain its significance. Thus, this nonselective inclusion of variables is not recommended for inves-

TABLE 1

Variables included in the stepwise regression analyses, white males aged 40–59 years, NHANES II, 1976–1980

Age*	Dietary iron†
Age-squared*	Dietary vitamin A†
Body mass index	Dietary vitamin C†
Dietary sodium†	Dietary thiamine†
Salt shaker sodium	Dietary riboflavin†
Dietary sodium × salt shaker sodium	Dietary niacin†
	Serum cholesterol†
Dietary potassium†	Serum vitamin C†
Dietary sodium-potassium ratio	Serum iron†
	Serum transferrin saturation
Dietary calcium†	Serum zinc†
Dietary phosphorus†	Serum copper†
Dietary protein†	Serum albumin†
Dietary fat†	Hemoglobin†
Dietary carbohydrate†	Red blood cell count
Dietary cholesterol†	Ethanol consumption/week†
Dietary saturated fatty acids†	Cigarettes smoked/day
	Total dietary grams†
Dietary oleic acid†	Total dietary calories†
Dietary linoleic acid†	

* This variable was forced into each regression to remove any possible age effects on blood pressure.

† The natural log and squared transformations of these variables were also included in the stepwise regression.

tigating the independent contributions of nutritional factors or blood analytes to blood pressure, and no conclusions are drawn in this analysis concerning the possible importance of any of these factors. However, if including so many terms and their nonlinear transformations in the stepwise regression does not appreciably alter the strength of the relationship between blood pressure and blood lead, this would provide considerable support for an independent relationship.

From the 87 nutritional and biochemical variables, the weighted stepwise regression selected five additional variables for diastolic pressure and six additional variables for systolic pressure using a 5 per cent significance level. These were used as the starting model for SURREGR, which additionally incorporates the survey design effects. For both systolic and diastolic pressures, one variable from the weighted stepwise regression failed to maintain significance at the 5 per cent level after the design effects were incorporated. The final regression results for systolic and diastolic blood pressures, after accounting for the weighting and design effects, are given in table 2. After including the nutritional variables, the blood analytes, and their curvilinear transformations, lead remained significantly associated ($p < 0.01$) with both systolic and diastolic blood pressures. The magnitude of this relationship, adjusted for the other significant variables, is depicted graphically in figures 1 and 2. Furthermore, segmented regression analyses indicated that there was not a threshold blood lead level in the data below which lead was not significantly related to blood pressure.

TABLE 2

Diastolic and systolic blood pressure multiple regression results, including both sampling weights and design effects, for white males aged 40–59 years, NHANES II, 1976–1980

Variable	Unstandardized regression coefficient	t statistic	Significance level
Diastolic blood pressure ($n = 564$; $r^2 = 0.23$)			
Age*	0.2768	0.17	0.864
Age-squared*	−0.0014	0.10	0.932
Body mass index	1.131	8.55	<0.001
Blood lead (ln scale)	3.954	2.83	0.008
Dietary potassium	−0.0018	4.92	<0.001
Hemoglobin	1.548	3.90	<0.001
Albumin	3.587	2.50	0.018
Dietary vitamin C†	1.838	4.65	<0.001
Systolic blood pressure ($n = 543$, $r^2 = 0.22$)			
Age*	1.311	0.57	0.572
Age-squared*	−0.0068	0.30	0.771
Body mass index	1.736	9.42	<0.001
Blood lead (ln scale)	8.436	3.24	0.003
Albumin	7.088	2.50	0.018
Dietary vitamin C†	2.411	3.84	<0.001
Dietary riboflavin†	−5.509	3.07	0.004
Dietary oleic acid†	3.992	2.49	0.018
Serum vitamin C†	−3.472	2.47	0.019

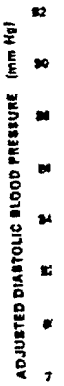
* This variable was forced into the regression to remove any possible age effects on blood pressure.

† The natural log (ln) transformation was selected in the stepwise regression.

As mentioned previously, the regression analysis was not directed at examining independent effects of nutritional and biochemical factors. However, it should be noted that each of the variables in the final systolic and diastolic models, except albumin and riboflavin, has previously been associated with blood pressure (1–4, 18, 19). Albumin may reflect ionized calcium which has been related to blood pressure (20).

In addition to the variables in table 1, several other variables were evaluated for their potential effect on the significance of blood lead: 1) whether or not on hypertensive medication, 2) amount of recreational and/or nonrecreational exercise, 3) residence in an urban versus rural area, 4) income greater versus less than $10,000, 5) educational level, 6) season of the year, 7) region of the country, 8) triceps skinfold thickness, and 9) family history of hypertension. None of these factors appreciably altered the relationship between blood pressure and blood lead.

In multiple regression analyses, another consideration is the possibility of significant interaction terms. To evaluate this



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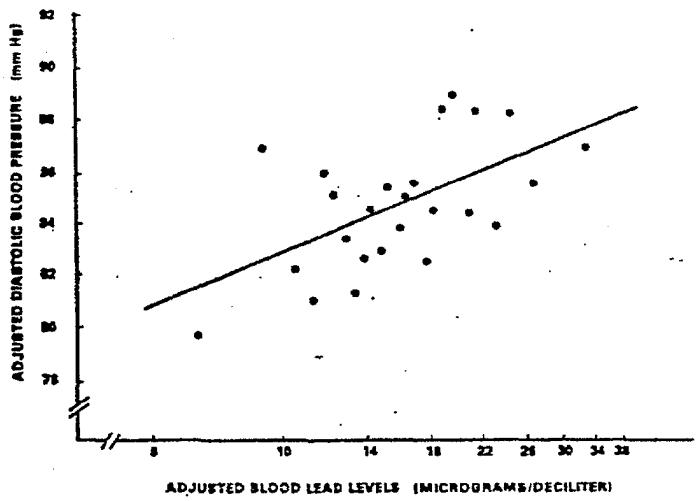

FIGURE 1. Adjusted diastolic blood pressure and adjusted blood lead levels for white males aged 40–59 years, NHANES II. Both blood pressure and blood lead have been adjusted by regression for the effects of age, age-squared, body mass index, and all other variables significant at the 5 per cent level (see table 2). The 564 observations have been reduced to 25 points for illustration. Each point is the mean blood pressure and mean blood lead of 22 or 23 consecutive observations, ordered by increasing blood lead levels. However, the plotted regression line reflects the slope coefficient obtained from the multiple regression analysis of all 564 points.

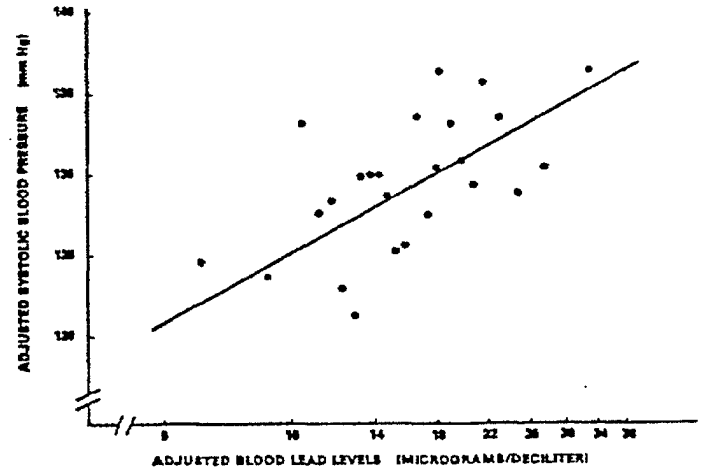

FIGURE 2. Adjusted systolic blood pressure and adjusted blood lead levels for white males aged 40–59 years, NHANES II. Both blood pressure and blood lead have been adjusted by regression for the effects of age, age-squared, body mass index, and all other variables significant at the 5 per cent level (see table 2). The 543 observations have been reduced to 25 points for illustration. Each point is the mean blood pressure and mean blood lead of 21 or 22 consecutive observations, ordered by increasing blood lead levels. However, the plotted regression line reflects the slope coefficient obtained from the multiple regression analysis of all 543 points.

possibility, an additional weighted stepwise regression analysis was done for systolic and diastolic blood pressures. The variables consisted of the linear interaction terms between the final variables in the model (shown in table 2) and the linear form of all the other variables originally selected for the initial stepwise regression (table 1). This amounted to running a stepwise regression with 162 interaction terms added to the final regression models for systolic and diastolic pressures. Using this large set of variables gave a high probability that some variables would enter at the 5 per cent level by chance. However, the purpose was not to determine if these variables were independently significant but rather to test further the significance and independence of the relationship between blood pressure and blood lead. As expected, several interaction variables entered the systolic and diastolic regressions, but in each regression, the lead coefficient varied less than 10 per cent and remained significant ($p < 0.015$).

Two other analyses were done to test this relationship further. First, the original weighted stepwise regression was extended to include variables through the 10 per cent significance level to see if marginally significant variables influenced the significance of lead. For both systolic and diastolic pressures, lead remained significant, and there was little change in the magnitude of the coefficient.

The second analysis was the most demanding test made of the independence of the relationship between blood pressure and blood lead. Models for diastolic and systolic blood pressures were fit by weighted stepwise regression to the original model variables (table 1), excluding lead. This gave all the other variables and their curvilinear transformations a maximal opportunity to explain variation that could also be explained by lead. After obtaining this new final model without lead, a single regression was run adding the lead variable to the variables of this new final model. For both systolic and diastolic pressures, lead was still statistically significant ($p < 0.016$), and the magnitude of the lead coefficient changed less than 10 per cent from those obtained in the original analysis (table 2). The results of these analyses indicated that the strength and independence of the relationship between blood pressure and blood lead were quite stable.

Public health implications

Two factors prompted analysis of the potential public health implications of the relationship of blood lead and blood pressure. First, if causally related, the regression results indicated that changes in blood lead levels formerly thought to be of little importance in adults may produce practically significant changes in blood pressure. Second, support for causality can be found in animal studies. In male rats, low blood lead levels (approximately 40 μg/dl) have been found to cause systolic blood pressure increases of 15–20 mmHg (21). The following public health implications are based on the assumption of causality, which is addressed later.

The general approach to estimating potential public health implications consisted of two steps: to calculate the change in blood pressure that might result from a specified change in blood lead levels and to use the Pooling Project and Framingham multiple logistic regression coefficients to calculate the change in incidence of cardiovascular and cerebrovascular events that would result from the lead-mediated changes in blood pressure. It is assumed in these calculations that the effect of lead is only on blood pressure.

The three outcomes examined were fatal and nonfatal myocardial infarction, fatal and nonfatal strokes, and death from all causes. Analyses specific for white males aged 40–59 years are available for fatal and nonfatal myocardial infarctions from the Pooling Project final report and for fatal and nonfatal strokes from the Framingham Study. Analysis of death from all causes is available for white males aged 40–54 years

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from Framingham, but the age range 55–59 years is not covered. For a specified follow-up period, each of these analyses provides the multiple logistic regression coefficients of risk factors (i.e., smoking, cholesterol, systolic and diastolic blood pressures, and age) for the outcome. The NHANES II data base also includes measurements of these risk factors for each white male in the 40- to 59-year age group.

Therefore, based on the multiple logistic regression coefficients, the predicted risk of each outcome for each white male aged 40–59 years in the NHANES II data can be calculated in a straightforward manner. The mean risk of each outcome for white males in this age group is obtained by taking the mean of the individual risks. If the survey sampling weights are included in calculating this mean risk, the result should be representative of white males who were aged 40–59 years from 1976 to 1980 (except for calculations involving death from all causes which covers ages 40–54 years). Multiplying the mean risk times the estimated number of US white males in this age group yields the predicted number of events.

The baseline risk calculation was performed using the NHANES II measured diastolic or systolic blood pressure for each individual. The effect of a specific increase (or decrease) in blood pressure on predicted risk of an outcome was measured by changing each individual's blood pressure by the specific blood pressure increase (or decrease) and recalculating each individual's predicted risk. The new mean predicted risk was then calculated using the survey sampling weights. For example, to measure the effect of a 1 mmHg increase in diastolic pressure on risk of fatal or nonfatal myocardial infarction, each individual's diastolic pressure was incremented 1 mmHg, and for each individual, a new predicted risk for myocardial infarction was calculated. Then, each individual risk was weighted by its survey sampling weight, and a new weighted mean risk was calculated which represented white males aged 40–59 years. Multiplying this new mean risk times the estimated number of US white males in this age group yielded the new predicted number of events.

This procedure was used to calculate the effect of blood pressure changes on incidence of serious outcomes. Over the period 1976–1980, mean blood lead levels for white adult males in the United States decreased 37 per cent (from 16.7 to 10.5 μg/dl) (22). From a public health perspective, an important calculation is the predicted effect this change in blood lead had on blood pressure and the incidence of serious outcomes which are related to blood pressure. Based on the Pooling Project logistic coefficients for white males aged 40–59 years, the 37 per cent decrease in blood lead levels resulted in a predicted 4.7 per cent decrease in the incidence of fatal and nonfatal myocardial infarctions over 10 years (table 3). Similarly, based on Framingham logistic coefficients, the blood lead decrease resulted in a predicted 6.7 per cent decrease in incidence of fatal and nonfatal strokes over 10 years. For death from all causes, the 37 per cent decrease in blood lead levels resulted in a predicted 5.5 per cent decrease over the subsequent 11.5 years. Calculations not incorporating the sample weights yield very similar per cent changes in incidence of serious outcomes; thus, the sample weighting has little effect on these estimates.

For white males aged 40–59 years, the effect of different mean blood lead levels on the predicted incidence of fatal and nonfatal myocardial infarctions, fatal and nonfatal strokes, and death from all causes is graphed in figures 3–5. From these graphs, the effect of changes in mean blood lead levels can be estimated.

Stepwise multiple logistic regressions were performed to determine if lead was a significant predictor of diastolic blood pressure greater than or equal to 90 mmHg. These stepwise logistic analyses found a similar set of statistically significant vari-

TABLE 3

Predicted change in the number of serious outcomes as a result of the 37% decrease in blood lead levels in adult white males aged 40–59 years, NHANES II, 1976–1980

	Follow-up period (years)	Predicted no. of events during follow-up period		Absolute difference in no. of events	% difference in no. of events
		Before 37% decrease in blood lead	After 37% decrease in blood lead		
Fatal and nonfatal myocardial infarctions*	10	1,638,200	1,560,900	77,300	4.7
Fatal and nonfatal strokes†	10	413,200	385,700	27,500	6.7
Death from all causes‡	11.5	1,353,600	1,279,700	73,900	5.5

* Men with a history of heart attack were excluded; based on Pooling Project multiple logistic coefficients for diastolic blood pressure, smoking, cholesterol, and age.

† Men with a history of previous stroke were excluded; based on Framingham multiple logistic coefficients for systolic blood pressure, smoking, cholesterol, and age.

‡ Data available only for ages 40–54 years; based on Framingham multiple logistic coefficients for diastolic blood pressure, smoking, and cholesterol.

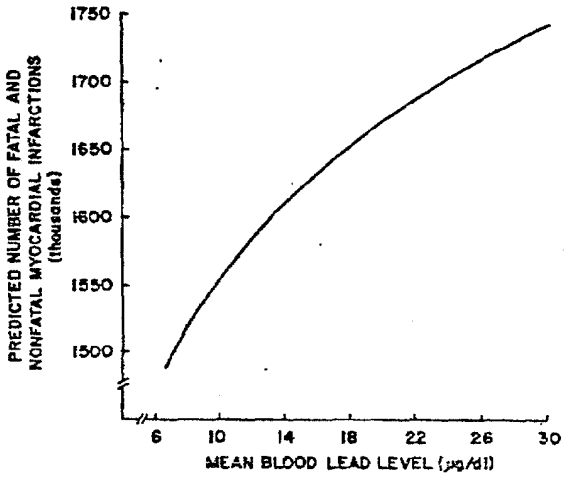

FIGURE 3. Predicted number of fatal and nonfatal myocardial infarctions for a follow-up period of 10 years (using the Pooling Project multiple logistic regression coefficients) and mean population blood lead levels for white males aged 40–59 years, NHANES II. Men with a history of a heart attack were excluded.

ables and found that blood lead was significant ($p < 0.01$). From these results, the 37 per cent decrease in blood lead levels yielded a predicted 1.3 million fewer white males aged 40–59 years with hypertension (diastolic ≥90 mmHg), a decrease of 17.5 per cent.

DISCUSSION

Lead is a toxic substance with no known physiologic function. Isotopic studies (23) have shown that the body lead burden of modern humans is about 500 times higher than that of preindustrial humans. Thus, although blood lead levels less than 30 μg/dl are designated as "low," they are actually high on a historical scale. The effect of current lead exposure on human health is therefore an important area of investigation.

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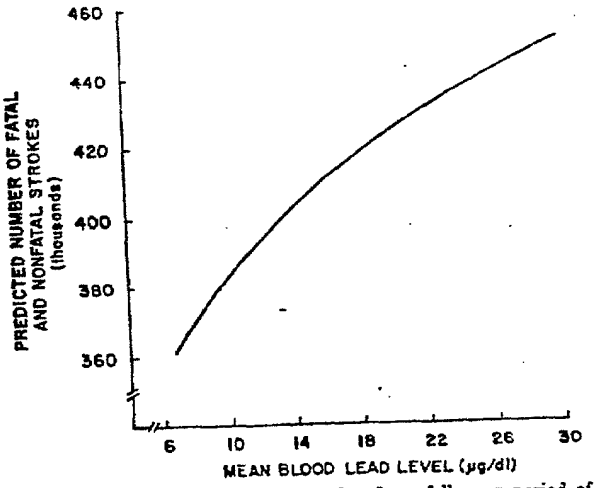

FIGURE 4. Predicted number of fatal and nonfatal strokes for a follow-up period of 10 years (using the Framingham multiple logistic regression coefficients) and mean population blood lead levels for white males aged 40–59 years, NHANES II. Men with a history of a stroke were excluded.

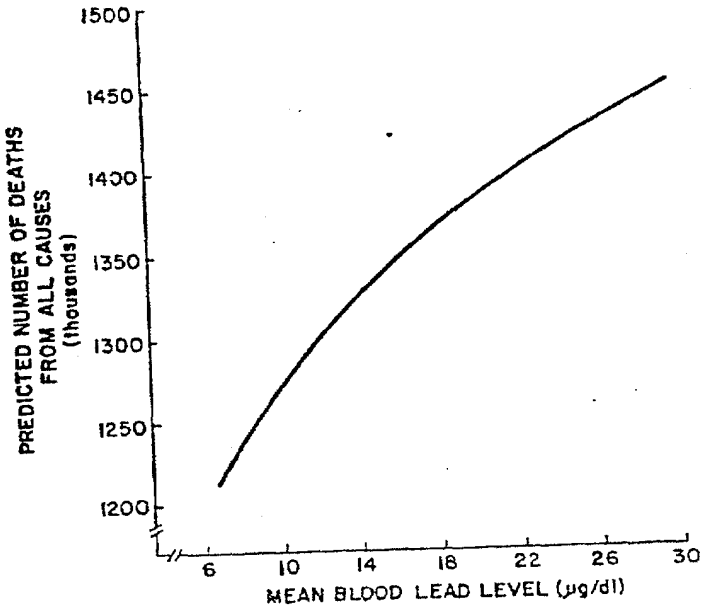

FIGURE 5. Predicted number of deaths from all causes for a follow-up period of 11.5 years (using the Framingham multiple logistic regression coefficients) and mean population blood lead levels for white males aged 40–54 years (rather than 40–59 years).

tries, whole blood lead was significantly related to both systolic and diastolic blood pressures in white males aged 40–59 years. In a conservative estimate of the strength and independence of this relationship, curvilinear transformations of almost all the variables were available for inclusion in the stepwise regressions to account for possible important nonlinear relationships. Moreover, a large set of interaction terms was included in the stepwise regression to account for their potential influence. Including both curvilinear transformations and interaction terms had little effect on the statistical significance or magnitude of the blood lead coefficient.

The possibility of omitting a relevant variable faces every epidemiologic study or survey. To provide the most conservative analysis, almost all the nutritional factors and blood biochemistries in the NHANES II data base were included in the stepwise analysis, whether or not they had previously been associated with blood pressure. Despite the inclusion of all these variables, there was little effect on the strength of the relationship between blood pressure and blood lead, and this extensive screening of variables provides strong support for an independent effect. It is still possible that a variable related to blood pressure has been omitted. To affect the results of this analysis, such an omitted variable would have to be related to both blood pressure and blood lead and not be well represented by any of the variables already in the stepwise regression. There is adequate unexplained variation in blood pressure for an omitted variable to be significantly related to blood pressure and still have a negligible effect on the relationship between blood pressure and blood lead. In addition to the variables in table 1, variables indicating residence, income status, exercise, use of hypertensive medication, educational level, season of the year, region of the country, triceps skinfold thickness, and family history of hypertension did not appreciably alter the relationship between blood pressure and blood lead. The possibility remains that an unknown omitted variable exerts a significant effect on both blood pressure and blood lead, but it is unlikely.

The strength and independence of the relationship between blood pressure and blood lead do not alone prove a causal association. A causal association between lead and blood pressure has been investigated in animal studies covering a large range of lead exposure. Of particular relevance to this analysis are studies in rats exposed to low levels of lead, an exposure insufficient to cause renal damage. Few studies are available which examined the effect of such low doses. Victery et al. (21) found that male rats with blood lead levels of about 40 μg/dl developed significant sustained increases in systolic blood pressure (15–20 mmHg) compared with controls. Using doses of lead much less than those causing rat blood lead levels of 40 μg/dl, Perry et al. (24) and Kopp et al. (25) also found increases in systolic pressure in rats. By contrast, Victery et al. noted that male rats with blood lead levels of 71 μg/dl showed no change in systolic pressure compared with controls, suggesting a biphasic blood pressure response to blood lead levels. A biphasic response could account for the results of animal studies that did not find a blood pressure effect at much higher doses of lead exposure. It may also help to clarify inconsistent epidemiologic findings of the effect of lead on blood pressure in persons without nephropathy who have mild to moderate as contrasted with marked elevations of blood lead.

Webb et al. (26) further investigated the mechanism of the effect of lead on blood pressure in male rats. They found that the blood pressure changes in male rats with low blood lead levels were associated with an increased vascular responsiveness to alpha adrenergic agonists, which could account for the pressor effect of lead. Animal studies can be summarized as indicating a causal relationship between relatively low blood lead levels and increases in blood

pressure. There is a suggestion of a biphasic blood pressure response which provides a rationalization for the findings of other animal and epidemiologic studies.

A statistically significant association between blood lead and blood pressure in men without renal impairment has been found in two other epidemiologic studies (27, 28). Also, hypertensive men with renal impairment have been found to have larger body stores of lead as measured by chelatable lead (29). There appears to be either a lesser association or no association between blood lead and blood pressure in women (5, 27). Additional epidemiologic studies will be useful in evaluating the consistency of current findings and in exploring the effect in females. Epidemiologic investigations will have to carefully consider statistical power, for blood lead measurements typically have a coefficient of variation of 10–20 per cent, and the expected blood pressure change for a blood lead change may be only a few mmHg. Although the results of the current study alone do not prove a causal relationship between low blood lead levels and blood pressure, our findings are consistent with current epidemiologic and animal studies, indicating that a causal relationship is probable.

Assuming a causal relationship, we predicted the effect of the recent 37 per cent decrease in blood lead levels of adult white males on the incidence of serious outcomes (table 3). The predicted decreases in fatal and nonfatal myocardial infarction (4.7 per cent), fatal and nonfatal strokes (6.7 per cent), and death from all causes (5.5 per cent) constitute substantial public health benefits. The relative changes in number of events with changes in mean blood lead levels are striking (figures 3–5), and in these calculations, lead has been assumed to affect only blood pressure. These calculations indicate that lowering the mean blood lead further would result in additional decreases in the number of predicted events.

Additional multiple logistic regression analyses were done to estimate the effect of the 37 per cent decrease in blood lead from 1976 to 1980 on the number of persons with diastolic pressures ≥90 mmHg. The Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure uses 90 mmHg as its cutoff to define hypertension and recommends treatment of diastolic pressures of 90 mmHg or higher (30). The 37 per cent decrease in mean blood lead levels resulted in a predicted 1.3 million fewer white males aged 40–59 years with hypertension (diastolic pressures ≥90 mmHg), a decrease of 17.5 per cent.

Finally, the absolute magnitude of the effect of lead on the incidence of these cardiovascular and cerebrovascular events in adult males is almost certainly underestimated since 1) persons were excluded who had a history of a myocardial infarction or stroke, and in these persons blood pressure increases likely increase the chance of a repeat event; 2) the calculation was limited to the age range 40–59 years (40–54 years for death from all causes); and 3) races other than white were not included.

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