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Lead, Blood Pressure, and Cardiovascular Disease in Men and Women

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Lead has been shown to be associated with elevated blood pressure in males in the NHANES II survey and in numerous other studies. This study confirms the association in males aged 20 to 74 and documents a significant, although weaker, association in females as well. Prospective cardiovascular disease studies such as the Framingham study indicate that increases in blood pressure should be associated with increased risk of cardiovascular disease. Using electrocardiogram data from NHANES II, this study confirms the expected association of lead with left ventricular hypertrophy ($p < 0.01$). Such an association with permanent cardiovascular changes adds weight to the blood pressure findings. The logistic risk coefficients from the Framingham study can be combined with the study's association between lead and blood pressure to examine its implication for more serious outcomes. The results suggest that a halving of the population mean blood lead level would reduce myocardial infarctions by approximately 24,000 events per year and incidence of all cardiovascular disease by over 100,000. These numbers suggest a small attributable risk compared to the vast incidence of cardiovascular disease in the U.S., but a large attributable risk compared to most environmental toxins. Several biological mechanisms have been identified, with different implications for the use of bone lead as an exposure measure.

Introduction

While numerous studies in animals and humans have implicated lead exposure as a factor in increasing blood pressure, they have often focused only on males and on restricted age ranges. Studies of direct cardiovascular outcomes have been hampered by the low relative risks implied by the blood pressure relationships that have been found. To address these issues, data from the Second National Health and Nutrition Examination Survey (NHANES II) were examined for males and females aged 20 years and older. The NHANES II included electrocardiograms as well as blood pressure measurements, and the association of lead with both outcomes was examined. This allowed a direct examination of the assumption that increased blood pressure due to lead will have cardiovascular implications.

Data and Methods

The Second National Health and Nutrition Examination Survey was conducted between February 1976 and February 1980. The sample was chosen to be representative of the civilian, noninstitutionalized U.S. population, aged 6 months to 74 years. Medical histories, serum biochemistries, and dietary questionnaires were obtained *(1)*. Blood lead levels were obtained on a subsample of 9932 subjects. Extensive analyses of the relationship between blood lead and blood pressure in males have been presented previously *(2–4)*, and they provide details of the medical history questionnaire, blood biochemistry methods, dietary information, and physical examinations.

Electrocardiograms were performed on all subjects aged 25 to 74 years using a standard 12-lead ECG. Results were digitally encoded and then classified according to the Minnesota Codes of Electrocardiographic Findings *(5)* using the Novacoder program of Dalhousie University *(6,7)*. Using variables identified as important in those earlier studies, the relationship between blood lead and blood pressure was examined in both males and females, aged 20 to 74 years. Table 1 shows the covariates considered in the analysis.

The blood pressure data were analyzed in stages. First, separate regressions were performed for males

Table 1. Variables considered in the regressions.

Age, years	ln (serum zinc)
Race[a]	ln (blood lead)
Sex[b]	Dietary potassium
Body mass index, kg/m^2	Dietary sodium
Cigarettes/day	Serum cholesterol
Tricep skinfold, mm	Height, m
Family history of hypertension	ln (dietary vitamin C)
Recreational exercise[c]	

[a] 2 = Black, 1 = white.
[b] Left ventricular hypertrophy regression: 2 = female, 1 = male.
[c] 1 = Little, 2 = moderate, 3 = substantial.

*U.S. Environmental Protection Agency, PM221, Office of Policy Analysis, Washington, DC 20460.

and females. Diastolic blood pressure was regressed on age, age^2, race, Quetelet's body mass index (weight/height^2), and the natural logarithm of blood lead. If lead was significant in this first step, then a stepwise regression was performed, using the variables shown in Table 1. An interaction term was used to assess the possibility of a racial difference in the effect of lead. Final models were estimated using SURREGR, a program that incorporates the design effects in the study (*8*).

The probability of left ventricular hypertrophy was modeled using logistic regression. Since the definition of left ventricular hypertrophy incorporates body habitus, body mass index and tricep skinfold were not included in these regressions. Stepwise logistic regression of the remaining covariates in Table 1 was used to identify a model. The design effects were incorporated using RTILOGIT (*9*). Because of the limited number of cases, sex differences in any lead effect were investigated using an interaction term. An interaction term was also used to test for racial differences.

Results

Blood lead was a significant predictor of blood pressure in both males ($p < 0.01$) and females ($p < 0.01$) in the first-stage regressions, controlling for age, race, and body mass index. In separate stepwise regressions for males and females, lead continued to be significantly related to diastolic blood pressure. The final models for blood pressure, incorporating the design effects of the survey, are shown on Table 2. While the coefficient of blood lead was lower in females than in males, the difference in magnitudes is not significant. This was confirmed in a regression with both sexes, using an interaction term to test for a different slope. The interaction was insignificant ($p > 0.30$). An interaction term for race was similarly insignificant. Race was not significant in the regression for males, presumably because racial differences in the biological risk factors explained the racial difference in blood pressure. Since blacks have higher blood lead levels than whites, the race term was forced into the regression to give a conservative estimate of the effect of lead.

Table 2. Regression results for diastolic blood pressure.

Variable	Coefficient	SE	*p*-value
Males			
Intercept	29.86	10.90	
Age	0.6073	0.0887	<0.0001
Age^2	−0.0057	0.0010	<0.0001
Body mass index	0.7312	0.0932	<0.0001
Race	1.549	0.8955	0.0934
Family history	2.543	0.4210	<0.0001
Cholesterol	0.0247	0.0071	0.0016
Blood lead[a]	2.928	1.002	0.0063
Height	12.89	3.251	0.0004
Cigarettes	−0.057	0.023	0.0183
Zinc	−4.37	1.491	0.0062
Tricep	0.0110	0.005	0.0490
Females			
Intercept	57.64	7.578	
Age	0.6135	0.1105	<0.0001
Age^2	−0.005	0.0012	0.0001
Body mass index	0.6857	0.0582	<0.0001
Race	2.408	0.7920	0.0047
Zinc	−5.54	1.646	0.0020
Family history	1.145	0.3688	0.0040
Blood lead[a]	1.640	0.6963	0.0247
Tricep	0.0084	0.0035	0.0203
Cholesterol	0.0113	0.0055	0.0477

[a] Natural logarithm.

Table 3. Logistic regression results: left ventricular hypertrophy.

Variable	Coefficient	SE	*p*-value
Intercept	−3.94	0.5081	
Age	0.0140	0.0052	0.0117
Race	1.357	0.2017	<0.0001
Sex	−1.01	0.1649	<0.0001
Lead	0.0283	0.0100	0.0087

Blood lead was also a significant predictor of left ventricular hypertrophy. Table 3 shows the logistic regression model, incorporating the design effects. The interaction terms for sex or race differences in the cardiovascular effects of lead were also insignificant ($p > 0.20$).

As in previous analyses (*2,3*), the natural logarithm of blood lead was more significant than blood lead in predicting blood pressure. This implies a relationship with a larger marginal impact of blood lead changes at low blood lead levels than at high blood lead levels. In contrast, the linear form of blood lead was more significant as a predictor of left ventricular hypertrophy.

Discussion

The existence of a strong association between blood lead and blood pressure across the entire adult age range has already been noted in males in this survey. This analysis demonstrates that a significant association is present in females as well. The association appears somewhat weaker in magnitude and in significance level than that for males. While most other epidemiology studies have focused on males, Rabinowitz et al. (*10*) have reported an association of lead with both blood pressure and pregnancy hypertension in females. Victery et al. (*11*) have reported a sex difference in the effect of lead on blood pressure in rats, with insignificant effects in females. However, Perry and Erlander (*12*) have reported a significant association in female rats, in a diet lower in calcium.

A large body of experimental data, both *in vivo* and *in vitro*, shows that lead increases blood pressure in several species of rats, pigeons, and dogs (*13–18*). These studies have also documented increased reactivity to alpha adrenergic stimulation (*14,16*) and an interaction with calcium metabolism (*15*). Many of these studies examined several dose levels, and Victery (*19*) has summarized them as indicating biphasic response, with a strong effect of low-level exposure that disappears at high levels. A similiar pattern has been seen

in the pressor effects of cadmium (*20*). These findings in the experimental literature are consistent with the logarithmic dose-response relationship found in this study.

Prospective studies of cardiovascular disease, such as the Framingham study (*21*), clearly demonstrate that the risk of cardiovascular disease varies continuously with blood pressure. No plausible reason exists to assume that increases in blood pressure due to lead exposure would not have the same impact. Studies of the use of drug therapy to reduce blood pressure have been more mixed, with the Hypertension Detection and Followup Study (*22*) finding significant reductions in risk, but not the MRFIT study (*23*). However, hypertensive medication has adverse side effects, including disturbances of potassium metabolism, that may counteract, in whole or part, the beneficial impacts of blood pressure reduction. Reducing lead exposure has no similar counter-risk, since lead has only harmful effects in the body. It therefore seems prudent to assume that reducing body lead burdens will reduce blood pressure and cardiovascular disease in both the new generation of adults who will not become exposed, as well as the current one, whose exposure will be reduced.

Nevertheless, direct evidence for a cardiovascular effect of lead would clearly strengthen these conclusions. The regression coefficients in Table 2 indicate that a halving of blood lead levels in the U.S. would reduce the mean male blood pressure by over 2 mm Hg, and the mean female blood pressure by over 1 mm Hg. The logistic risk coefficients from the Framingham study predict that these changes would result in about 24,000 fewer myocardial infarctions per year, and over 100,000 fewer cases of cardiovascular disease. While these are large numbers compared to most risk assessments for environmental toxins, they represent relative risks of about 1.05 due to the high background rate of these outcomes. Such relative risks are unlikely to be detected in any prospective study. Electrocardiogram abnormalities indicative of left ventricular hypertrophy represent an early indicator of cardiovascular disease that is more common than myocardial infarctions. Left ventricular hypertrophy is also a prevalence, rather than incidence measure. This increases the power to detect a direct cardiovascular impact of lead. The finding of a significant association between blood lead levels and left ventricular hypertrophy in both men and women leaves little doubt that lead exposure is not merely raising blood pressure but producing the expected cardiovascular impacts.

While cardiovascular effects of lead intoxication have long been noted, ECG outcomes have been studied infrequently at the exposure levels of current concern. Kirkby and Gyntelberg (*24*) noted a 20% increase ($p < 0.01$) in ischemic changes, as coded on the Minnesota Codes, in lead workers compared to controls matched on age, race, sex, height, weight, alcohol consumption, and smoking. Kopp (*25*), in an ECG study of rats, found prolonged PR intervals, depressed contractility and protein phosphorylation, and high energy phosphate levels. Hejtmancik and Williams (*26*) have reported increased susceptibility to arrhythmias in lead-exposed rats. While not directly parallel, Khera (*27*) did note increased blood and urine lead levels in cardiovascular patients compared to hospital controls.

Potential Mechanisms and Bone Lead

The experimental studies provide more than simple biological support for the epidemiological findings. They also provide insight into several possible biological mechanisms for the effect of lead on blood pressure. The two major modes of action identified are in the calcium metabolism of the vascular smooth muscle and renal effects mediated through the renin-angiotensin system. In addition, direct cardiovascular effects may also occur.

Piccinini and co-workers (*18*) found that lead induced contraction and hyper-reactivity in perfused rat tail arteries. Tissue analysis indicated the lead-exposed vascular smooth muscle cells had increased free cytosolic calcium and increased total calcium stores. This is consistent with the finding that lead increases cellular calcium concentration in brain capillaries (*28*), neurons (*29*), hepatocytes (*30*), and other tissues. Hyper-reactivity has also been noted by Iannaconne and co-workers (*31*), Carmignani et al. (*14*), Boscolo and Carmignani (*31*), and Webb and associates (*16*). These findings suggest a mechanism with increased intracellular calcium stores, leading to increased release of calcium in response to stimulation, and hence increased contractility via calcium's role in mediating muscle contraction. Supporting this hypothesis is the observation of Chai and Webb (*32*) that methoxamine-induced contractions in the tail arteries of lead-exposed rats were less sensitive to calcium channel blockers and relaxed at a slower rate than unexposed arteries.

A second mode of action for lead in disturbing the calcium-mediated control of vascular reactivity and tension may be via disturbance of protein kinase C metabolism. Markovac and Goldstein (*33*) have shown that lead activates protein kinase C in rat brain microvessels. Protein kinase C is involved in the phosphorylation of proteins involved in contraction (*34*). Recent studies by Chai and Webb (*32*) have shown that isolated strips of rabbit tail artery contracted in response to lead. This contractile response was enhanced by protein kinase C activators, but attenuated by a selective inhibitor of protein kinase C.

Both of the above mechanisms seem dependent on the current concentration of lead at the membrane or in the cytosol of the smooth muscle cell. This suggests that the appropriate measure of exposure is one that is relatively contemporaneous. Blood lead is such a measure. The entire effect cannot be considered instantaneous, since both Victery and colleagues (*11*) and Perry and Erlanger (*12*) found that rat blood pressure did not reach its equilibrium elevation until several months after blood lead levels equilibrated. Bone lead measurements that are targeted to shorter residence com-

partments, possibly including trabecular bone, may be a superior measure of exposure, but this remains to be seen.

A mechanism more consistent with cumulative exposure measures postulates permanent kidney changes resulting in effects on the renin-angiotensin system. The animal and human data on the effect of lead on this system are confusing, with findings of both increased and decreased plasma renin activity following lead exposure. Vander and associates (*35*) have postulated an elevation of plasma renin activity upon initial exposure, followed by an eventual reduction after chronic exposure. This hypothesis comes closest to making sense out of the conflicting data and accords with the finding of Boscolo and Carmignani (*14*) of a similar pattern in human exposure.

All or some of the above mechanisms may be important in lead-induced hypertension, but they are consistent with different averaging times for the best measure of exposure. It seems most likely that short-term exposure and altered calcium metabolism are the most important pathways for blood pressure elevation. Cardiovascular outcomes seem likely to vary with duration as well as level of blood pressure change, suggesting a more cumulative exposure measure would be appropriate for them. Finally, it should be noted that Revis et al. (*15*) found lead associated with atherosclerosis in pigeons. These findings, plus some of the direct cardiovascular effects noted by Kopp (*25*), also suggest that cumulative measures of lead may be important for assessing cardiovascular disease. Final resolution of the appropriate exposure measure will await studies that use all of them.

REFERENCES

1. National Center for Health Statistics. Plan and Operation of the Second National Health and Nutrition Examination Survey 1976–1980. Vital and Health Statistics, Series 1, No. 15, NCHS, Washington, DC, 1981.
2. Pirkle, J. L., Schwartz, J., Landis, J. R., and Harlan, W. R. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. Am. J. Epidemiol. 121: 246–258 (1985).
3. Schwartz, J. The relationship between blood lead and blood pressure in the NHANES II survey. Environ. Health Perspect. 78: 15–22 (1988).
4. Harlan, W. R., Landis, J. R., Schmouder, R. L., Goldstein, N. G., and Harlan, L. C. Blood lead and blood pressure relationship in the adolescent and adult U.S. population. J. Am. Med. Assoc. 253: 530–534 (1985).
5. Blackburn, H., Keys, A., Simonson, E., Rautaharju, P.M., and Punsar, S. The electrocardiogram in population studies: a classification system. Circulation 21: 1160–1175 (1960).
6. Wolf, H. K., MacInnis, P. J., Stock, S., Helppi, R. K., and Rautaharju, P. M. The Dalhousie Program: a comprehensive analysis program for rest and exercise electrocardiograms. In: Computer Applications on ECG and VCG Analysis (C. Zyweitz and B. Schneider, Eds.), North Holland Press, Amsterdam, 1973, pp. 231–240.
7. Rautaharju, P. M., Broste, S. K., Prineas, R. J., Eifler, W. F., Crow, R. S., and Furberg, C. D. Quality control procedures for the resting electrocardiogram in the Multiple Risk Factor Intervention Trial. J. Control. Clin. Trials 7: 465–655 (1986).
8. Shah, B. V. SURREGR. Research Triangle Institute, Research Triangle Park, NC, 1982.
9. Shah, B. V. RTILOGIT. Research Triangle Institute, Research Triangle Park, NC, 1987.
10. Rabinowitz, M., Bellinger, D., Leviton, A., Needleman, H., and Schoenbaum, S. Pregnancy hypertension, blood pressure during pregnancy, and blood lead levels. Hypertension 10: 447–451 (1987).
11. Victery, W., Vander, A. J., Shulak, J. M., Schoeps, P., and Julius, S. Lead, hypertension, and the renin-angiotensin system in rats. J. Lab. Clin. Med. 99: 354–362 (1982).
12. Perry, H. M., and Erlanger, E. J. Pressor effects of chronically feeding cadmium and lead together. In: Trace Substances in Environmental Health, Vol. 12 (D. D. Hemphill, Ed.), University of Columbia, Columbia, MO, 1978, pp. 268–275.
13. Iannaccone, A., Carmignani, M., and Boscolo, P. Cardiovascular reactivity in the rat following chronic exposure to cadmium and lead. Ann. First Super Sanita 17: 655–660 (1981).
14. Carmignani, M., Boscolo, P., Ripanti, G., and Finelli, G. N. Effects of chronic exposure to cadmium and lead on some neurohumoral mechanisms regulating cardiovascular function in the rat. In: Proceedings of the Fourth International Conference on Heavy Metals in the Environment, Vol. 1, CEP Consultants, Edinburgh, 1983, pp. 557–560.
15. Revis, N. W., Zinsmeister, A. R., and Bull, R. Atherosclerosis and hypertension induced by lead and cadmium ions: an effect prevented by calcium ion. Proc. Natl. Acad. Sci. USA 8: 6494–6498 (1981).
16. Webb, R. C., Winquist, R. J., Victery, W., and Vander, A. J. In vivo and in vitro effects of lead on vascular reactivity in rats. Am. J. Physiol. 214: H211–216 (1981).
17. Skoczynska, A., Juzwa, W., Smolok, R., Szechinski, J., and Behal, F. J. Response of the cardiovascular system to catecholamines in rats given small doses of lead. Toxicology 39: 275–289 (1986).
18. Piccinini, F., Favalli, L., and Chiari, M. C. Experimental investigations on the contraction induced by lead in arterial smooth muscle. Toxicology 8: 43-51 (1977).
19. Victery, W. Evidence for effects of chronic lead exposure on blood pressure in experimental animals: an overview. Environ. Health Perspect. 78: 71–76 (1988).
20. Perry, H. M., Jr., Erlanger, M. W., and Perry, E. F. Hypertension following chronic very low dose cadium feeding. Proc. Soc. Exp. Biol. Med. 156: 173–176 (1977).
21. Shurtleff, D. Some characteristics related to the incidence of cardiovascular disease and death: Framingham study, 18-year follow up. Section 30, DHEW Publication No. (NIH) 74–599, Department of Health Education and Welfare, Washington, DC, 1974.
22. Hypertension Detection and Followup Program Cooperative Group. The effect of treatment on mortality in mild hypertension. N. Engl. J. Med. 307: 976–980 (1983).
23. Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. J. Am. Med. Assoc. 248: 1465–1477 (1982).
24. Kirkby, H., and Gyntelberg, F. Blood pressure and other cardiovascular risk factors of long-term exposure to lead. Scand. J. Work Environ. Health 11: 15–19 (1985).
25. Kopp, S. J., Baker, J. C., D'Agrosa, L. S., and Hawley, P. L. Simultaneous recording of His bundle electrogram, electrocardiogram, and systolic tension from intact modified Langendorff rat heart preparations I: effect of perfusion time, cadmium, and lead. Toxicol. Appl. Pharmacol. 46: 475–487 (1978).
26. Hejtmancik, M. R., and Williams, B. J. Effect of chronic lead exposure on the direct and indirect components of the cardiac response to norepinephrine. Toxicol. Appl. Pharmacol. 51: 239–245 (1979).
27. Khera, A. K., Wibberley, D. G., Edwards, K. W., and Waldron, H. A. Cadmium and lead levels in blood and urine in a series of cardiovascular and normotensive patients. Int. J. Eviron. Studies 14: 309–312 (1980).
28. Goldstein, G. W. Lead encephalopathy: the significance of lead inhibition of calcium uptake by brain mitochondria. Brain Res. 136: 185–188 (1977).
29. Kim, C. S., O'Tuama, L. A., Cookson, S. L., and Mann, J. D. The

effects of lead poisoning on calcium transport by brain in 30-day-old albino rabbits. Toxicol. Appl. Pharmacol. 52: 491–496 (1980).
30. Pounds, J. G. Effect of lead intoxication calcium homeostasis and calcium-mediated cell function: a review. Neurotoxicology 5: 295–332 (1984).
31. Boscolo, P., and Carmignani, M. Neurohumoral blood pressure regulation in lead exposure. Environ. Health Perspect. 78: 101–106 (1988).
32. Chai, S. and Webb, R. C. Effects of lead on vascular reactivity. Environ. Health Perspect. 78: 85–89 (1988).
33. Markovac, J. and Goldstein, G. W. Picomolar concentrations of lead stimulate brain protein kinase C. Nature 334: 71–73 (1988).
34. Rasmussen, H., Takuwa, Y., and Park, S. Protein kinase C in the regulation of smooth muscle contraction. FASEB J. 1: 177–185 (1987).
35. Vander, A. J. Chronic effects of lead on the renin-angiotensin system. Environ. Health Perspect. 78: 77–83 (1988).