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# Blood Pressure and Blood Lead Concentration in Bus Drivers

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San Francisco bus drivers have an increased prevalence of hypertension. This study examined relationships between blood lead concentration and blood pressure in 342 drivers. The analysis reported in this study was limited to subjects not on treatment for hypertension ( $n = 288$ ). Systolic and diastolic pressures varied from 102 to 173 mm Hg and from 61 to 105 mm Hg, respectively. The blood lead concentration varied from 2 to 15  $\mu\text{g}/\text{dL}$ . The relationship between blood pressure and the logarithm of blood lead concentration was examined using multiple regression analysis. Covariates included age, body mass index, sex, race, and caffeine intake. The largest regression coefficient relating systolic blood pressure and blood lead concentration was 1.8 mm Hg/ $\ln(\mu\text{g}/\text{dL})$  [90% C. I., -1.6, 5.3]. The coefficient for diastolic blood pressure was 2.5 mm Hg/ $\ln(\mu\text{g}/\text{dL})$  [90% C. I., 0.1, 4.9]. These findings suggest effects of lead exposure at lower blood lead concentrations than those concentrations that have previously been linked with increases in blood pressure.

## Introduction

An increased prevalence of cardiovascular disease, including hypertension, has been noted in transit worker populations (1-9). There has been a parallel concern about lead exposure from vehicular exhaust (10-13). The relationship between lead exposure and blood pressure has been a recent focus of attention (14-18). Both experimental and observational studies corroborate a causal relationship between low-level lead exposure and increased blood pressure (19); however, this relationship has not been studied in transit workers.

Unadjusted hypertension prevalences in San Francisco bus drivers were 47.4/100 for blacks and 40.2/100 for whites, using the criteria systolic pressure > 140 mm Hg or diastolic pressure > 90 mm Hg (9). Stratifying on age and race, these rates were 1.3 to 1.9 times greater than rates for males in the National Health and Nutrition Examination Survey (NHANES) II study; the Alameda County Hypertension Control Program

study; and men undergoing pre-employment screening for bus driver positions (9).

## Subjects and Methods

Drivers were approached at their biennial medical examination; 342 of 456 agreed to participate. Three blood pressure measurements were taken by mercury sphygmomanometry (diastolic phase V). Differences between the means of the first and second measurements (designated as contrasts) and their 99% confidence intervals for all subjects were -0.1 [-1.3, 1.0] mm Hg for systolic blood pressure and 0.04 [-0.7, 0.8] mm Hg for diastolic blood pressure. Contrasts between the average of the first two measurements and the third were 2.6 [1.5, 3.7] and 0.8 [0.1, 1.5] mm Hg, respectively. These latter contrasts were small to moderate in magnitude but statistically significant. Subsequently, the average of the first two measurements (AVSYS12, AVDIA12), the third measurement (SYS3, DIA3), and the average of all three (AVESYS, AVEDIA) were used as separate outcome indicators in examining the relationship between blood pressure and blood lead concentration. Additional data (age, race, sex, etc.) were abstracted from the clinic record as well as a ques-

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tionnaire designed specifically for this study.

From each participant, 10 mL of blood was drawn directly into polypropylene tubes containing Li-heparin and frozen for later analysis. Blood lead concentrations were determined at the Toxicology Laboratory, San Francisco General Hospital Medical Center, by atomic absorption spectrophotometry (20). This laboratory participates in the Centers for Disease Control (CDC) interlaboratory standards control program for lead analysis.

Two samples were analyzed from each specimen and recorded if the absorbance values were within 10% of each other. If the values were not within 10% a third sample was analyzed, and the closest two absorbance values were chosen. The mean absolute difference between the two samples was 0.51 µg/dL. Five percent of these differences exceeded 1.34 µg/dL.

Quality control checks using bovine blood standards obtained from the CDC were performed after every second to fifth specimen. The standard control value was 19.0 µg/dL. The mean and standard deviation of these checks were 18.7 ± 1.28 µg/dL ( $n = 122$ ). Control values determined within a given standards curve showed a significant and continuous downward trend due to the impact of degradation of the graphite furnace on the absorbance signal. Each unknown specimen blood lead concentration (PbB) was adjusted by the quality controls ( $QC_1, QC_2$ ) bounding it by

$$PbB_{adj} = PbB \left[ \frac{19.0}{\frac{1}{2}(QC_1 + QC_2)} \right]$$

Twenty-two external quality controls were incorporated into the specimen collection. The mean and standard deviation of these were 4.2 ± 0.9 µg/dL.

Analysis of variance for unequal sample sizes and multiple regression methods were used to assess relationships (21). Subjects treated for hypertension were excluded. Precision of estimated parameters was assessed using 90% confidence intervals. This level was chosen because the blood lead concentration/blood pressure relationship has already been established in a number of population studies (14–18). Also, the lower bound of the interval effectively functions as a 95% test of statistical significance for the directional hypothesis of a positive relationship. If the lower confidence limit is greater than 0, then the one-tailed  $p$  value is < 0.05. Bootstrap methods were used to validate the magnitude and precision of the estimated relationship between blood pressure and blood lead concentration in selected cases (22,23).

## Results

Table 1 illustrates the age, race, sex, and body mass index (BMI) characteristic of the study sample. Table 2 presents the univariate distributions of blood pressure and blood lead concentration. The distribution of blood lead concentration was remarkably low considering

**Table 1. Descriptive statistics of features characterizing the study sample.**

Variable	<i>n</i>	Mean	SD	Range
Age, years				
Males	261	42.7	7.13	30.6–64.7
Females	27	40.3	6.89	27.9–54.5
BMI, <sup>a</sup> kg/m <sup>2</sup>				
Males	259	27.2	4.30	18.6–45.3
Females	27	30.2	6.71	19.7–45.5
Race				
Asians	59			
Blacks	161			
Hispanics	29			
Whites	38			

<sup>a</sup>BMI, body mass index.

the subjects were city bus drivers. The range varied from 2 to 15 µg/dL.

The age-adjusted mean and standard error, and median for the average systolic (AVESYS) and average diastolic (AVEDIA) blood pressures among four ordered categories of blood lead concentration are presented in Table 3. There was no apparent trend, although for both systolic and diastolic blood pressure the lowest average values were in the lowest quartile of blood lead concentration.

Multiple regression analyses are presented in Tables 4 and 5. AVSYS12, AVDIA12; SYS3, DIA3; and AVESYS, AVEDIA were used as dependent variables in separate analyses. The logarithmic transformed blood lead concentration was used in these models. The justification for doing so has been to normalize the blood lead concentration distribution. While the logarithmic transformation appears to accomplish this, it also imposes a nonlinear scale transformation that may not be justified. However, results are presented in this manner for consistency with other published studies (14,15).

Covariates included in the model were age, the square of age, race, sex, body mass index nested in sex, and frequency of caffeine consumption. There is evidence that recent caffeine ingestion affects blood pressure measurements (24).

Because multiple regression models are prone to bias from outliers, the influence of each observation on the magnitude of the regression coefficient relating blood lead concentration and blood pressure was examined. The magnitude of this influence is measurable by a standardized parameter available in the PROC REG procedure in SAS (21).

Single, but different, observations were identified as outliers for systolic and diastolic measures. These outliers produced values of the influence parameter that were 6.47 and 6.99 standard deviations removed from the mean influence value for SYS3 and AVDIA12, respectively. The next set of most influential points were 3.0 to 3.4 standard deviations from the mean for all models involving the different blood pressure variables as outcomes.

The effect of excluding these observations is presented

**Table 2. Univariate distributions of blood pressures and blood lead concentration in subjects not currently treated for hypertension.<sup>a</sup>**

Measurement	Percentiles								
	1%	5%	10%	25%	50%	75%	90%	95%	99%
AVESYS, <sup>b</sup> mm Hg	102	107	109	115	123	132	141	148	173
AVEDIA, <sup>c</sup> mm Hg	61	67	70	75	81	85	91	95	105
PbB, µg/dL	2.3	3.6	3.9	4.8	6.4	8.1	9.4	10.8	15.5

<sup>a</sup>The reader is cautioned not to relate variables within a percentile. *n* = 288.

<sup>b</sup>AVESYS, average systolic pressure.

<sup>c</sup>AVEDIA, average diastolic pressure.

**Table 3. Distribution of average systolic and diastolic blood pressures in four categories of blood lead concentration.**

Measurement	PbB quartile	Mean PbB, µg/dL	<i>n</i>	Mean ± SE	Mean ± SE	Median
					age adj	
AVESYS, mm Hg	1	4.0 ± 0.08	72	123.0 ± 1.58	123.3 ± 1.55	121.7
	2	5.7 ± 0.05	72	125.7 ± 1.52	125.9 ± 1.54	125.3
	3	7.2 ± 0.05	72	128.8 ± 1.77	126.0 ± 1.54	122.7
	4	9.9 ± 0.26	72	124.8 ± 1.47	124.2 ± 1.55	122.7
AVEDIA, mm Hg	1	4.0 ± 0.08	72	79.0 ± 1.03	79.3 ± 1.04	80.0
	2	5.7 ± 0.05	72	80.9 ± 0.96	81.0 ± 1.03	80.3
	3	7.2 ± 0.05	72	82.0 ± 1.20	81.9 ± 1.03	81.3
	4	9.9 ± 0.26	72	81.4 ± 0.94	81.2 ± 1.04	82.3

**Table 4. Regression coefficient relating systolic BP and ln(PbB).<sup>a</sup>**

Coefficient, mm Hg/ln(µg/dL)			90% C. I.	Residual df
AVSYS12	SYS3	AVESYS		
0.32			[-3.51, 4.16]	276 <sup>b</sup>
	1.95		[-1.76, 5.65]	276 <sup>b</sup>
		0.86	[-2.86, 4.58]	276 <sup>b</sup>
-0.34			[-4.00, 3.32]	265
	1.07		[-2.46, 4.61]	265
		0.63	[-3.40, 3.66]	265
0.28			[-3.34, 3.89]	264 <sup>c</sup>
	1.83		[-1.63, 5.28]	264 <sup>c</sup>
		0.79	[-2.68, 4.27]	264 <sup>c</sup>

<sup>a</sup>Adjusted for age, body mass index, sex, race, and caffeine intake.

<sup>b</sup>No adjustment for any covariate.

<sup>c</sup>Outlier removed.

**Table 5. Regression coefficient relating diastolic BP and ln(PbB).<sup>a</sup>**

Coefficient, mm Hg/ln(µg/dL)			90% C. I.	Residual df
AVDIA12	DIA3	AVEDIA		
2.25			[-0.25, 4.74]	276 <sup>b</sup>
	1.79		[-0.68, 4.25]	276 <sup>b</sup>
		2.09	[-0.34, 4.53]	276 <sup>b</sup>
2.01			[-0.38, 4.39]	265
	1.49		[-0.87, 3.85]	265
		1.83	[-0.49, 4.16]	265
2.60			[0.19, 5.01]	264 <sup>c</sup>
	2.16		[-0.22, 4.54]	264 <sup>c</sup>
		2.45	[0.10, 4.80]	264 <sup>c</sup>

<sup>a</sup>Adjusted for age, body mass index, sex, race, caffeine intake.

<sup>b</sup>No adjustment for any covariate.

<sup>c</sup>Outlier removed.

in the last section of Tables 4 and 5. The excluded observations were on a subject with a low blood lead concentration and a high blood pressure in the case of the systolic pressure, and on a subject with high blood lead concentration but low blood pressure in the case of the diastolic pressure. There was insufficient information from clinic records to exclude the subjects on known medical grounds, although the subject excluded from models involving diastolic blood pressure had sickle cell trait and a history of hypertension in both parents.

Upon examining systolic pressure (Table 4), the largest adjusted regression coefficient appeared to be 1 to 2 mm Hg/ln(µg/dL), but so imprecisely estimated [approximate 90%, C. I., -2.0, 5.0] as to suggest no relationship. Table 5 presents the results for diastolic blood pressure. The adjusted regression coefficient was 2.2 to 2.6 mm Hg/ln(µg/dL) [90%, C. I., 0.1, 4.9].

Figures 1 and 2 present distributions of regression coefficients obtained by bootstrap simulations using SYS3 and AVDIA12, respectively, as dependent variables. A bootstrap simulation is a cross-validation procedure with two basic steps. First, subjects are randomly picked from the study sample with replacement for a total number equal to the sample size used in the model of interest. Thus, some subjects may be chosen more than once, and some not at all. The data from these chosen subjects are used in the multiple regression model of interest to generate estimates of the regression coefficients.

Second, this procedure is repeated a set number of times (e.g., 1000), with the coefficient(s) of interest saved. The mean value of a particular coefficient and its standard deviation are internally valid estimators of the original sample's estimated regression coefficient and standard error (22,23).

No subjects were excluded from the respective sampling frames for this simulation. A mean coefficient of

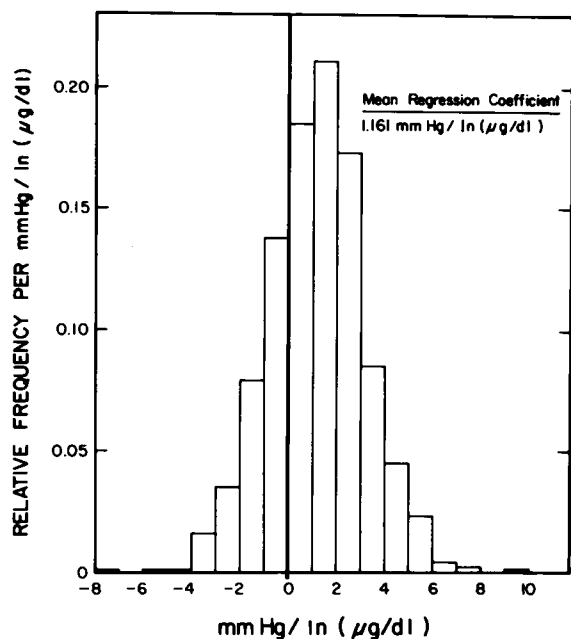


FIGURE 1. Distribution of regression coefficients from a multiple regression model relating SYS3 to  $\ln(\text{PbB})$  using a bootstrap simulation (1000 repetitions).

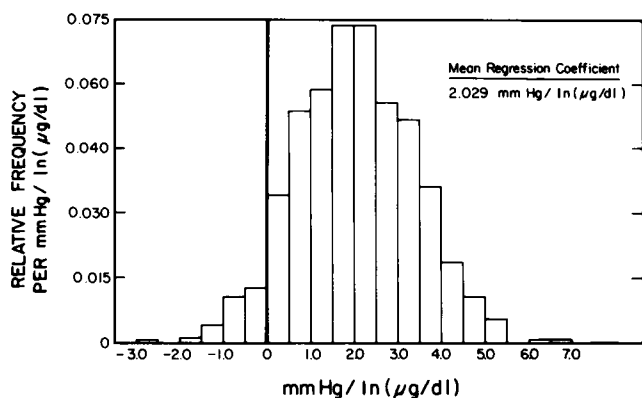


FIGURE 2. Distribution of regression coefficients from a multiple regression model relating AVDIA12 to  $\ln(\text{PbB})$  using a bootstrap simulation (1000 repetitions).

1.16 mm Hg/ $\ln(\mu\text{g/dL})$  was obtained for SYS3. Twenty-seven percent of the coefficients were less than 0. A mean coefficient of 2.03 mm Hg/ $\ln(\mu\text{g/dL})$  was obtained for AVDIA12. Six percent of the coefficients were less than 0.

## Discussion

The blood lead concentrations in these subjects were quite low (median: 6.4  $\mu\text{g/dL}$ , range: 2–15  $\mu\text{g/dL}$ ). This contrasts with the higher ranges reported in the National Health and Nutrition Examination Survey (NHANES) II study of 8 to 35  $\mu\text{g/dL}$  (15), and a similar, though slightly lower, range in the British Regional Heart (BRH) Study (17).

In spite of these low values, evidence for an independent relationship between blood pressure and blood lead concentration was found. This relationship was most apparent with diastolic blood pressure [2–3 mm Hg/ $\ln(\mu\text{g/dL})$ , 90% C.I.: [0.1, 4.9]], but uncertain with systolic blood pressure [1–2 mm Hg/ $\ln(\mu\text{g/dL})$ , approximate 90% C. I., -2.0, 5.0].

The regression coefficient predicting diastolic blood pressure was comparable to those reported for the NHANES II and BRH Studies. Reanalysis of these data by the Environmental Protection Agency (25) and Pocock et al. (26) yielded coefficients of 1.4 to 2.7 mm Hg/ $\ln(\mu\text{g/dL})$  for NHANES II, and 1.8 mm Hg/ $\ln(\mu\text{g/dL})$  for the BRH Study.

It is unclear whether alcohol consumption should be included as a covariate in these models relating blood pressure and blood lead concentration. There is evidence that alcohol consumption is associated with elevated blood pressure (27). However, it is not clear whether this association is directly causal (28); whether it is indirectly causal, being mediated by some impact on increased lead activity (29–32); or whether it reflects lead contamination of alcoholic beverages (33,34). Adjusting for alcohol consumption could result in undesirable overcontrol of lead exposure.

The impact of including a variable for alcohol consumption derived from questionnaire data (grams of ethanol per week) on the regression coefficients relating systolic and diastolic blood pressure, and blood lead concentration is a reduction of approximately 0.3 mm Hg/ $\ln(\mu\text{g/dL})$  in the magnitudes of the coefficient. It is not clear what such a change in the regression coefficient means. It may be that the unadjusted relationship is confounded by alcohol consumption, and thus inclusion of a measure of alcohol intake adjusts for this confounding. However, it may be that alcohol intake acts as an indirect indicator of a lead effect on blood pressure, and thus inclusion of this variable in the regression model acts to overcontrol for lead activity in its relationship with blood pressure. Indeed, it is possible that both processes are operable. Resolution of this dilemma rests with a better understanding of the biological relationships among lead, alcohol, and blood pressure.

## Mechanisms

Most lead in the body is stored in the bone. Bone deposition effectively sequesters lead from susceptible organs. However, this depository, upon resorption, also acts as a source of internal exposure to these same organs.

Bone resorption is under the control of parathyroid hormone (PTH). Thus, PTH activity may be a determinant in the equilibrium between bone and soft tissue lead concentration. Serum PTH concentrations and chelated urinary lead excretion have been shown to be increased in hypertensive patients with gouty

nephropathy when compared to age-matched controls with glomerulonephritis (35). An unselected population is not readily comparable to the patients in this clinical study; however, these findings, coupled with established knowledge that chronic, low-level lead exposure is related to blood pressure and indicators of calcium metabolism and that lead sequestered in the kidney affects renal tubule reabsorption of calcium (36) and phosphate (37), suggest that effects on parathyroid hormone metabolism may be relevant to people without overt clinical disease.

The causal relationship between hypertension and renal failure is not readily apparent. Lead accumulation appears to play a role in both conditions (38). One scenario suggests that chronic lead accumulation causes hypertension, and hypertension leads to renal failure. A contrasting scenario suggests lead accumulation in the kidney leads to subclinical renal dysfunction, which in turn causes hypertension. It is conceivable that both scenarios interact in a positive feedback mechanism, leading to progressive hypertensive disease and renal failure. Chronic lead accumulation, internal lead mobilization from bone resorption by the action of PTH, and lead-induced alternations in kidney tubule reabsorption of electrolytes affecting PTH elaboration are interactive factors requiring further investigation.

## Reliability Issues

There are three aspects to reliability in lead/hypertension research. The first is how reliable the operational indicators of lead accumulation and blood pressure status reflect the underlying biological processes. The second is how reliably the given operational indicators are actually measured by the study design. The third relates to the reliability of the laboratory analysis procedure.

Single cross-sectional blood lead concentration and blood pressure measurements are indirect indicators of the true effect of chronic lead accumulation on cardiovascular function, and relate weakly to actual lead activity and pathophysiologic effect. Given that the operational indicators of blood pressure status and lead accumulation are truly related, then the public health importance of this relationship is probably much greater than suggested by published studies (19). The unreliability of these measures (single blood pressure measurements and blood lead concentrations) in reflecting the underlying biological process is not addressed by improving measurement precision. This can be resolved only by more specific tools of measurement.

The second aspect of reliability relates to measurement precision. Single measurements are relatively imprecise indicators of steady-state blood lead concentration and blood pressure status. Individual blood lead concentrations can vary over a period of weeks due to changing environmental exposures. A similar

problem exists with blood pressure measurement, which is affected by endogenous catecholamines and by proximate caffeine and nicotine consumption. The question arises whether, and under what conditions, this second reliability problem is important.

In cross-sectional studies the magnitude of a relationship (either a correlation or a regression coefficient) can be biased to zero if the measurement variables are unreliable. The magnitude of this bias depends on the ratio of the within-subjects variance to the between-subjects variance (39). This issue has been particularly important in nutritional studies (40–44). The ratio has been reported to be as high as 10 to 20, although it is usually 0.3 to 4 (41).

The biasing effect of this ratio is given for the correlation coefficient by

$$\frac{\rho_{DF}}{\rho_{xy}} = \left[ \left(1 + \frac{\sigma_w^2}{n_1 \sigma_b^2}\right) \left(1 + \frac{\xi_w^2}{n_2 \xi_b^2}\right) \right]^{-\frac{1}{2}}$$

where  $\rho_{DF}$  is the estimated population correlation coefficient;  $\rho_{xy}$  is the true value,  $\sigma_w^2$  and  $\sigma_b^2$  are the within-subjects and between-subjects variances for the variable  $x$ ;  $\xi_w^2$  and  $\xi_b^2$  are the respective variances for the variable  $y$ ; and  $n_1$  and  $n_2$  are the number of repeated measurements of  $x$  and  $y$  for each subject. Reliability is improved by increasing the number of measurements within a subject, not by increasing the number of subjects.

Reliability bias can be examined in this study of bus drivers by estimating the variance ratios for blood pressure and blood lead concentration. An inexact estimate of the within-subject variation is obtained for blood pressure from the three measures taken during the examination. The variance ratios are 0.12 for both systolic and diastolic pressures. An observed correlation coefficient involving either measure would be biased low by about 2% from this source of variation. However, other sources of variation (e.g., day-to-day, etc.) could be much larger, and thus bias the relationship substantially more.

Unreliability in the blood lead concentration measurement cannot be assessed directly from the data on bus drivers. It can be approximated using the data of Cope et al. (45). Up to seven repeated measurements of blood lead concentration over a period of 3 months were made in five refinery workers exposed to alkyl and inorganic lead. The average within-subjects variance derived from this data is  $0.01 \ln^2 (\mu\text{g/dL})$ . The interindividual variance from the bus driver study is  $0.14 \ln^2 (\mu\text{g/dL})$ . The variance ratio of 0.07 would result in a bias of about -3.0%.

The combined impact of unreliability in both variables from these approximations would be about -5.0%. Although this bias appears to be minor, without direct assessment of within-subjects variation in the context of a specific study design, it could be much larger.

The third reliability issue relates to laboratory analysis. Blood lead concentration measurements are notoriously subject to bias from contamination. Imprecision problems can be manifest when the blood lead concentrations within a study group are low and limited in range. Demonstration of a relationship between blood pressure and blood lead concentration in this study depended intimately on laboratory techniques that enhanced precision and compensated for internal biases. Future work that involves such low blood lead concentrations must document the precision of the analytic technique, especially in studies that fail to demonstrate relationships.

## Conclusions

Sizable proportions of the population are exposed to low levels of lead and develop hypertension. Even though the relationship between blood lead concentration and blood pressure appears to be weak, the effect attributable to lead exposure may be substantial due to the magnitude of these proportions.

It is unclear whether a reduction in lead accumulation in the adult hypertensive population would result in a substantial decrease in hypertension. The blood pressure elevation attributable to lead exposure could effectively be irreversible given that the toxicokinetics of lead distribution limit lead excretion from the body and/or damage to organ systems resulting in hypertension is irreparable. [Lead effects on kidney function, which may play a role in lead-related hypertension, appear to be reversible after chelation therapy (46).] However, a reduction in lead exposure in major segments of the population who have yet to accumulate lead (i.e., children) would have a substantial impact in reducing hypertensive disease in the adult population of tomorrow.

This study of adult bus drivers demonstrates relationships between blood lead concentration and blood pressure at the lowest blood lead concentrations reported to date. Deleterious effects on cognitive development associated with similar blood lead concentration levels have recently been reported in children (47). Findings such as these in both adults and children at exceedingly low levels of lead exposure suggest a need to reassess what constitutes an acceptable level of exposure in the population.

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