AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 40:63–72 (2001)

Blood Pressure, Left Ventricular Mass, and Lead Exposure in Battery Manufacturing Workers

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Background *Although debate about the relationship between lead and blood pressure has focused on low environmental lead levels, industrial exposure remains a concern.*
Methods *We measured blood pressure and left ventricular mass (LVM) in 108 battery manufacturing workers, and calculated cumulative and historic average measures of blood lead.*
Results *Diastolic pressure increased with increasing lead levels, with a significant ($P = 0.04$) 5 mmHg difference in mean pressure between the highest and lowest cumulative exposure levels. Diastolic pressure increased with the log of cumulative lead ($P = 0.06$). Both hypertension (defined as currently medicated or systolic >160 mmHg or diastolic >95 mmHg) and LVM increased nonsignificantly with increasing lead exposure (P-values ≥ 0.17 for hypertension and ≥ 0.20 for LVM).*
Conclusions *We found a small effect of blood lead on diastolic blood pressure, particularly for a cumulative measure of exposure, but no convincing evidence of associations between lead and other blood-pressure-related outcomes.* Am. J. Ind. Med. 40:63–72, 2001. *Published 2001 Wiley-Liss, Inc.*†

KEY WORDS: lead; blood pressure; hypertension; cardiovascular disease; battery manufacturing

INTRODUCTION

Since the mid-1980s, many studies have been conducted to examine the association between lead exposure and blood pressure. The literature continues to show discrepant findings among studies, reflecting methodological differences in study design and data analysis strategies, and differences in levels of lead exposure. The focus of many studies has been on relatively low levels of lead exposure in the general population. Although levels of exposure in many industries have declined over the last few decades, blood lead levels in persons with occupational exposure remain above those in the general population and are of continuing concern [Centers for Disease Control and Prevention, 1999]. Workplace-based studies can provide opportunities for improving our understanding of the relationship between lead and blood pressure. In many workplaces, historic levels of exposure are well documented in plant-based biological monitoring programs and workers have experienced a wide range of exposures, which may help to clarify any dose-response relationship.

In this study, we assessed the effects of long-term lead exposure (calculated both as a cumulative and a time-weighted average exposure) on blood pressure (as both a continuous and a dichotomous outcome) and its consequences (increased LVM).

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Accepted 30 January 2001

Published 2001 Wiley-Liss, Inc.
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MATERIALS AND METHODS

Subjects

The study was conducted at a facility manufacturing specialty batteries for telecommunications, electric utility, health care, and other applications. Although the battery specifications have varied over the years the plant has been in operation, the basic process of producing lead-acid batteries has remained relatively unchanged. Eligible study subjects included all workers at the facility who were hired between 1 January 1960 and 31 December 1983, worked 10 or more years in battery production, and were currently working for or had retired from the company. All participants provided written informed consent. The study protocol was approved by the Institutional Review Board of the National Institute for Occupational Safety and Health.

Lead Exposure

Blood lead testing was carried out by the company since the early 1970s. Since then, several different laboratories did the analysis, and no records were available to describe the changes in analytic methods. The company's blood lead records were obtained for all eligible subjects. Information in these records was used to calculate three measures of lead exposure, CBLI (cumulative blood lead index), TWA-BPb (time-weighted average blood lead), and mean blood lead for the year preceding the study (for those still working at the battery plant).

The CBLI was calculated as follows: $\mathrm{CBLI} = \sum \frac{1}{2}(\mathrm{B_i} + \mathrm{B_{i+1}})\Delta\mathrm{t}$, where $\mathrm{B_i}$ and B_{i+1} are the ith and $(\mathrm{i}+1)$th blood lead measurements, respectively, and Δt is the time between measurements [Somervaille et al., 1988]. The units of measurement for CBLI are μg/dl-yr (micrograms per deciliter-years). The TWA-BPb was calculated as follows: TWA-BPb = CBLI/t, where t is the total time in the plant. The units of measurement for TWA-BPb are μg/dl. The 1-year mean blood lead was the mean of all measurements taken in the year before the study, expressed as μg/dl.

Some subjects started work before regular, widespread lead monitoring began. After reviewing the work histories, we found that 23 subjects had worked in lead-exposed jobs for more than 1 year before their first blood lead measurement. The median duration of employment before testing was 2.2 years, with a range 1.1–11.2 years. For these 23 individuals, a starting blood lead level of 12 μg/dl was assigned. This value was the median entry blood lead level for all workers who had been tested upon first employment at the company. A second blood lead level was assigned 3 months after the starting date. For each subject, the second assigned value was equal to their own median blood lead level during the first 2 years of monitoring. For 15 subjects, the job worked during the period of missing data was the same as that worked during the subsequent 2 years. For four subjects, the job was different but the department was the same, and for four subjects, the job and the department were different or unknown. We also assigned ending blood lead values for all subjects. A blood lead value equal to the last known value was assigned for the study date (for current employees) or termination date (for retirees).

Questionnaire

All subjects completed a self-administered questionnaire. The questionnaire included the following major areas: demographic characteristics, family history of cardiovascular disease, medical history (including use of antihypertensive medication and other medication that may affect blood pressure), hobbies that might involve lead exposure, and history of cigarette smoking and alcohol consumption.

Blood pressure

Following the procedures of the American Heart Association, on 2 consecutive days, trained observers measured blood pressure of subjects not taking antihypertensive medication [American Heart Association, 1993]. Using a standard mercury sphygmomanometer (W.A. Baum Co., Inc., New York, Desk Model with V-Lock® Cuff), we measured seated blood pressure in millimeters of mercury (mmHg) with a blood pressure cuff appropriate for arm circumference. For each day, the mean of two measurements taken 30 s apart on the right arm was computed, then the mean of the measures for the 2 days was computed. Systolic and diastolic readings were recorded to the nearest 2 mmHg as the first and fifth Korotkoff sounds, respectively. Hypertension was defined as systolic pressure ≥ 140 mmHg, or diastolic pressure ≥ 90 mmHg [JNC, 1993], or self-reported use of antihypertensive medication. We also considered an alternative hypertension definition, using higher cutoff points for blood pressure, specifically, systolic greater than 160 mmHg or diastolic greater than 95 mmHg [Hu et al., 1996], or self-reported use of antihypertensive medication.

In addition to the blood pressure measurements made by the trained observers, subjects not taking antihypertensive medication measured their blood pressure at home over a 24-h period. Blood pressure was measured with a digital sphygmomanometer (HEM 705CP Omron Healthcare, Inc., Vernon Hills, IL). Study participants were instructed to take measurements at five specified times throughout the day. At each time, they took two measurements following a standard protocol. The monitors had the capability to print the stored results. We checked the data for physiologically improbable values (systolic <70 or >260, diastolic <40 or >150, or pulse pressure <20 or >150) and for observations with unreliable measurements (more than 15 mmHg difference in

paired values of systolic or diastolic pressure). No physiologically improbable values were found. Observations with substantially different values were deleted from analysis. This included 52 (13%) of 396 observations for systolic pressure and 23 (6%) of 396 observations for diastolic pressure.

Anthropometry

Trained observers measured standing height and weight without shoes, and triceps, waist, and hip circumference. All measurements were taken twice and the average was calculated. A random 10% sample was selected for repeat measurement on another day. For the 12 participants who were measured on 2 days, the difference between the paired measurements was not statistically significant, with a mean difference of 0.18 kg for weight, −0.25 cm for height, 0.62 mm for triceps, 1.31 cm for waist, and 0.74 cm for hip. Body mass index (BMI) was evaluated as weight (kg) divided by height (m) squared (m^2). BMI was classified as follows: normal, $BMI < 27.3$ for females, $BMI < 27.8$ for males; overweight, $27.3 \leq BMI < 32.3$ for females, $27.8 \leq BMI < 31.1$ for males; or obese, $BMI \geq 32.3$ for females, $BMI \geq 31.1$ for males [National Center for Health Statistics, 1987]. Body surface area (BSA) was calculated as follows: $BSA = (weight^{0.425})\ (height^{0.725})\ (0.007184)$ [Grossman and Baim, 1995].

Echocardiography

An M-mode, two-dimensional echocardiogram and a limited Doppler echocardiogram of the mitral valve were obtained from all subjects. Standardized operating procedures were followed for obtaining a technically adequate study and for ensuring subject comfort and safety. Trained echocardiographers administered the echocardiograms. Measurements were made by a cardiologist (KS) or by one of two echocardiographers under her supervision. The cardiologist reread a sample of 20 echocardiograms measured by the echocardiographers; the correlation between her readings was 0.96 for one echocardiographer and 0.98 for the other. Echocardiograms were considered technically adequate if the left ventricular endocardium and cavity, left atrium size, and valves were delineated clearly. Measurements of chamber size were made according to the criteria of the American Society of Echocardiography [Sahn et al., 1978]. Left ventricular mass was estimated according to the Penn Convention [Devereaux and Reicheck, 1977].

Statistical Analysis

The main goal of our analysis was to assess the relationship between four health outcomes—hypertension, diastolic pressure, systolic pressure, and left ventricular mass—and two measures of occupational lead exposure—CBLI and TWA-BPb. Because initial modeling showed nonlinear relationships between certain of the outcome variables and the continuous forms of the exposure variables, we categorized the lead exposure variables based on their tertiles. For the hypertension outcome, we used logistic regression to estimate odds ratios and 95% confidence intervals corresponding to the tertiles of lead exposure, using the first tertile as the reference group. We also examined the relationship between hypertension and continuous forms of the exposure variables, considering both untransformed and log-transformed versions of exposure. For diastolic pressure, systolic pressure, and left ventricular mass, we used linear regression models to calculate adjusted response means for each exposure tertile. We assessed the statistical significance of the difference between adjusted means, using the first tertile as the reference group. We also examined the relationship between these continuous outcomes and continuous forms of the exposure variables, considering both untransformed and log-transformed version of exposure. In all analyses, *P*-values less than or equal to 0.05 were considered statistically significant.

To identify potential confounders, we first evaluated nonoccupational factors (age, sex, race, family history of hypertension, alcohol consumption, cigarette smoking, diabetes, body mass index, and other measures of body fat, including triceps circumference and waist to hip ratio) by assessing their relationship with each of the outcome and exposure measures. Based on the findings of this bivariate analysis, we decided to consider a common set of factors for all subsequent multivariable analyses. The common set of factors included age (<45, 45–54, 55+), BMI (normal, overweight, obese), sex (male, female), and family history of hypertension (no, yes).

In addition to the main analyses, we also examined the relationship between systolic and diastolic pressure, and recent blood lead level (i.e., the mean level in the year prior to the measurement of blood pressure). This analysis was done among actively employed subjects only. All statistical analyses were performed using SAS (Version 6.12).

RESULTS

Subjects

Eligible subjects included 166 active employees (66%), nine employees on long-term disability (4%), and 77 retirees (30%). Of these 252 employees, 114 (45%) agreed to participate. The participation rate was greater among active (54%) than among retired (30%) or disabled (11%) employees and was correspondingly higher among employees less than 60 years of age (54%) than those age 60 and above (30%). The participation rate did not differ by sex.

We had some data to compare participants and nonparticipants with respect to hypertension, blood pressure, and lead exposure. Forty (29%) of the 138 eligible employees who did not participate in the medical study gave us some information about hypertension. Fourteen respondents (35%) said they were currently taking medicine for high blood pressure. This was higher than the percentage taking antihypertensive medication among participants (26%). We also had blood pressure data from the company's medical records. Because of routine blood pressure screening and periodic physical exams over the years, many employees had their blood pressure measured at work. A blood pressure measurement since 1991 was available for 83 participants (73%) and 72 nonparticipants (52%). (1991 was the most recent year for which the majority of employees had blood pressure data.) Using the most recent measurement for each individual since 1991, the records showed that for participants and nonparticipants, respectively, the mean (range) systolic pressures were 128 mmHg (92–160) and 129 mmHg (98–170) and the mean (range) diastolic pressures were 83 mmHg (60–110) and 85 mmHg (60–112). Blood lead data were available for 98 nonparticipants (71%). Comparing participants to nonparticipants, the median CBLI was slightly higher in participants (629 vs. 590 μg/dl-yr), but the median TWA was similar in the two groups (30 vs. 31 μg/dl).

Based on reviews of the work history and blood lead data, six subjects were excluded from further analysis. Two were excluded because we had neither work history nor blood lead data, and four were excluded because blood lead data were missing for more than 50% of their work time in lead-exposed jobs. Four of the six met our definition of hypertension (described below) based on use of antihypertensive medications (three) or measured blood pressure (one). All data reported below are based on analysis of the remaining 108 subjects.

To assess the possible effects of assigning blood lead values for 23 individuals missing data in the early years of their tenure in the plant, we repeated our final regression models excluding these individuals. The results were not substantially different from those presented below.

Measures of Occupational Lead Exposure

To describe the distribution of blood lead levels in the plant, we calculated the median level within each year for each individual. The overall mean of these medians was 31 μg/dl, ranging from 2 to 93. Blood lead levels, however, declined over time. Mean (and range) blood lead levels for each 5-year period from 1970 to 1994 were as follows: 1970–1974: 47 μg/dl (10–93), 1975–1979: 36 μg/dl (10–74), 1980–1984: 31 μg/dl (8–65), 1985–1989: 26 μg/dl (2–50), and 1990–1994: 24 μg/dl (5–63).

The mean CBLI was 642 μg/dl-yr, the range was 138–1446. We defined three CBLI groups (tertiles) of equal size (n = 36) as follows: 1st tertile, $138 \leq \text{CBLI} < 505$; 2nd tertile $505 \leq \text{CBLI} < 747$; 3rd tertile, $747 \leq \text{CBLI} < 1447$.

The mean TWA-BPb was 30 μg/dl, the range was 12–50. We defined three TWA-BPb groups (tertiles) of equal size (n = 36) as follows: 1st tertile, $12 \leq \text{TWA-BPb} < 25.6$; 2nd tertile, $25.6 \leq \text{TWA-BPb} < 34$; 3rd tertile, $34 \leq \text{TWA-BPb} < 50.3$.

Distribution and Effects of Nonoccupational Factors

The distribution of some of the nonoccupational factors considered as potential confounders varied by level of occupational lead exposure (Table I). Subjects ranged in age from 36 to 73 years, with the majority above the age of 45. Although CBLI is a cumulative measure of exposure, age was not directly related to CBLI; the lowest CBLI tertile had the largest percentage of workers above the age of 55. Overall, 43% of subjects were women, but the sex distribution differed markedly by level of occupational lead exposure. The percentage of women decreased with increasing exposure (both CBLI and TWA-BPb), from about 70% in the lowest exposure tertiles to about 10% in the highest exposure tertiles. Two-thirds of subjects reported a family history of hypertension. For both measures of occupational exposure, the middle tertile had the highest percentage of subjects with a positive family history. High body mass index was common, with about 60% of subjects being classified as overweight or obese. Although the proportions of abnormal body mass varied with both measures of occupational lead exposure, the pattern was irregular.

As noted before, we used a common set of covariates for all multivariable models. In the final models, age, body mass index, and family history of hypertension were statistically significant predictors of hypertension and systolic pressure, family history was a statistically significant predictor of diastolic pressure, and gender and body mass index were statistically significant predictors of left ventricular mass. In the results presented below, we focus on the relationship between occupational lead exposure and the health outcomes, all adjusted for each of these four covariates.

Comparison of Observer-Measured and Self-Measured Blood Pressure

Self-measured blood pressure was positively correlated with the mean observer-measured blood pressure (systolic: $r = 0.81$, $P < 0.01$; diastolic: $r = 0.78$, $P = 0.01$). On average, the observer-measured blood pressure was higher than the self-measured blood pressure. The mean difference

TABLE I. Distribution of Nonoccupational Factors Among Battery Manufacturing Workers by Level of Lead Exposure

		CBLI (μg/dl-yr)[a]			TWA (μg/dl)[b]		
	Total (n = 108)	138–504 (n = 36)	505–746 (n = 36)	747–1447 (n = 36)	12–25 (n = 36)	26–33 (n = 36)	34–50 (n = 36)
Age (yrs %)							
36–44	19	28	19	11	31	8	19
45–54	41	25	44	53	28	56	39
55–73	40	47	36	36	42	36	42
Race (%)							
Nonwhite	63	67	56	67	61	69	58
White	37	33	44	33	39	31	42
Sex (%)							
Female	43	72	42	14	69	47	11
Male	57	28	58	86	31	53	89
Diabetes (%)							
No	94	89	94	97	97	86	97
Yes	6	11	6	3	3	14	3
Family history of hypertension (%)							
No	34	42	19	42	44	19	39
Yes	66	58	81	58	56	81	61
Family history of cardiovascular disease (%)							
No	29	36	17	33	42	17	28
Yes	71	64	83	67	58	83	72
BMI[c] (%)							
Normal	39	33	39	44	33	31	53
Overweight	31	31	44	19	39	33	22
Obese	30	36	17	36	28	36	25
Cigarette smoking status (%)							
Never	38	31	42	42	39	42	33
Former	34	39	31	33	33	33	36
Current	28	31	28	25	28	25	31
No. current cigarettes per day, mean (range)	4 (0–40)	5 (0–20)	4 (0–20)	4 (0–40)	4 (0–20)	3 (0–20)	5 (0–40)
No. alcoholic drinks per week in past year, mean (range)	4 (0–28)	4 (0–28)	6 (0–28)	3 (0–18)	3 (0–28)	5 (0–28)	3 (0–18)
Ever drank 5+ drinks a day (%)							
No	80	81	78	81	78	83	78
Yes	20	19	22	19	22	17	22

[a] CBLI: cumulative blood lead index (μg/dl-yr).
[b] TWA-BPb: time-weighted average blood lead (μg/dl).
[c] Overweight: males, $27.8 \leq \text{BMI} \leq 31.1$, females, $27.3 \leq \text{BMI} < 32.3$; obese: males, $\text{BMI} \geq 31.1$, females, $\text{BMI} \geq 32.3$.

between measurements was 2.3 mmHg for diastolic pressure ($P < 0.01$) and 2.5 mmHg for systolic pressure ($P < 0.05$). Because of the differences by measurement method, we initially conducted separate analyses for each method of blood pressure measurement. The results of these analyses were remarkably similar. Thus, the final analyses presented below involve only the observer-measured blood pressures.

TABLE II. Associations Between Hypertension and Cumulative and Historical Average Blood Lead Levels Among Battery Manufacturing Workers

	Hypertension systolic > 140 or diastolic > 90 mmHg			Hypertension systolic > 160 or diastolic > 95 mmHg		
	No. (%) of cases	OR[a]	95% CI[b]	No. (%) of cases	OR	95% CI
CBLI[c]						
Tertiles						
138–504	18 (50)	1.0 (referent)	—	10 (28)	1.0 (referent)	—
505–746	15 (42)	0.39	0.11–1.33	11 (31)	1.05	0.29–3.81
747–1447	18 (50)	0.99	0.27–3.63	13 (37)	2.71	0.70–11.39
Continuous exposure						
Untransformed	$P = 0.25$[e]			$P = 0.42$		
Log-transformed	$P = 0.26$			$P = 0.17$		
TWA-BPb[d]						
Tertiles						
12–25	17 (47)	1.0 (referent)	—	10 (28)	1.0 (referent)	—
26–33	19 (53)	0.56	0.16–1.79	13 (36)	1.02	0.30–3.49
34–50	15 (42)	0.79	0.22–2.79	11 (31)	1.44	0.38–5.85
Continuous exposure						
Untransformed	$P = 0.75$			$P = 0.41$		
Log-transformed	$P = 0.74$			$P = 0.28$		

[a] OR (odds ratio): adjusted for age, body mass index, sex, and family history of hypertension.
[b] CI: confidence interval.
[c] CBLI: cumulative blood lead index (μg/dl-yr).
[d] TWA-BPb: time-weighted average blood lead (μg/dl).
[e] P value for the regression coefficient of the continuous exposure variable.

Hypertension

Fifty-one subjects (47%) met the standard clinical definition of hypertension, 26 based on use of antihypertensive medication and 25 based on measured blood pressure. The percentage of subjects with hypertension varied inconsistently by level of lead exposure (Table II). The prevalence of hypertension was 50, 42, and 50% and 47, 53, and 42%, for the 1st, 2nd, and 3rd tertiles of CBLI and TWA-BPb, respectively. For both CBLI and TWA-BPb, the adjusted odds ratios for the 2nd and 3rd tertiles were below 1 and the 95% confidence intervals included 1. There was also no evidence that hypertension increased with increasing lead levels when exposure was expressed as a continuous variable (all P values ≥ 0.25). We reran the final model including only those subjects who were hypertensive based on measured blood pressure (i.e., were not taking antihypertensive medication). The odds ratios for each level of CBLI and TWA remained below 1.

Thirty-four subjects met the more conservative definition of hypertension, 26 based on use of antihypertensive medication and eight based on measured blood pressure. Using this definition of hypertension, the risk of hypertension was elevated in the 3rd tertile for both CBLI (OR = 2.71) and TWA-BPb (OR = 1.44). There was, however, no convincing evidence that hypertension increased with increasing lead levels when exposure was expressed as a continuous variable (all P values ≥ 0.17).

Blood Pressure

Eighty-one subjects (75%) were not taking antihypertensive medication at the time of the study and had their blood pressure measured.

Diastolic pressure ranged from 60 to 104 mmHg, with a mean of 80. Adjusted mean diastolic pressure increased from 77 to 81 to 82 mmHg and from 79 to 80 to 81 mmHg for the 1st, 2nd, and 3rd tertiles of CBLI and TWA-BPb, respectively (Table III). For CBLI, the 5 mmHg difference between the 1st and 3rd tertiles was statistically significant ($P = 0.04$). Analysis of lead exposure as a continuous variable also showed some evidence of an association

TABLE III. Associations Between Diastolic Blood Pressure, Systolic Blood Pressure, Left Ventricular Mass, and Cumulative and Historical Average Blood Lead Levels Among Battery Manufacturing Workers

	Mean (SE)[a]		
	Diastolic pressure (mmHg)	Systolic pressure (mmHg)	Left ventricular mass/ body surface area (g/m^2)
CBLI[b]			
Tertiles			
1st: 138–504	77 (1.7)	134 (3.2)	98 (4.4)
2nd: 505–746	81 (1.7)	127 (3.2)	105 (4.1)
3rd: 747–1447	82 (1.7)[c]	132 (3.3)	106 (4.4)
Continuous exposure			
Untransformed	$P = 0.26$[e]	$P = 0.43$	$P = 0.54$
Log-transformed	$P = 0.06$	$P = 0.49$	$P = 0.20$
TWA-BPb[d]			
Tertiles			
1st: 12–25	79 (1.7)	134 (3.3)	98 (4.5)
2nd: 26–33	80 (1.8)	130 (3.3)	103 (4.1)
3rd: 34–50	81 (1.7)	129 (3.3)	108 (4.4)
Continuous exposure			
Untransformed	$P = 0.14$	$P = 0.72$	$P = 0.37$
Log-transformed	$P = 0.10$	$P = 0.84$	$P = 0.30$

[a] Mean (SE: standard error): adjusted for age, body mass index, sex, and family history of hypertension.
[b] CBLI: cumulative blood lead index (μg/dl-yr).
[c] $P = 0.04$. This indicates a statistically significant difference between this mean and the mean for the lowest tertile. All other comparisons of means yielded $P > 0.10$.
[d] TWA-BPb: time-weighted average blood lead (μg/dl).
[e] P value for the regression coefficient of the continuous exposure variable.

between diastolic pressure and lead exposure, with stronger evidence for CBLI (log-transformed, $P = 0.06$) than TWA-BPb (log-transformed, $P = 0.10$).

Systolic pressure ranged from 101 to 177 mmHg, with a mean of 131. Adjusted mean systolic pressure varied from 134 to 127 to 132 mmHg and from 134 to 130 to 129 mmHg for the 1st, 2nd, and 3rd tertiles of CBLI and TWA-BPb, respectively (Table III). There was also no evidence that systolic pressure increased with increasing lead levels when exposure was expressed as a continuous variable (all P values ≥ 0.40).

Left Ventricular Mass

One hundred five subjects (97%) had technically adequate echocardiograms from which we could measure left ventricular mass. Mean LVM (adjusted for body surface area) was 109 g/m^2 (range: 54–205) in men and 95 g/m^2 (range: 45–138) in women. Adjusted mean left ventricular mass increased from 98 to 105 to 106 g/m^2 and from 98 to 103 to 108 g/m^2 for the 1st, 2nd, and 3rd tertiles of CBLI and TWA-BPb, respectively (Table III). The increase in left ventricular mass with increasing lead levels, expressed as continuous variables, was not statistically significant (all P values ≥ 0.20).

Blood Pressure and Recent Lead Exposure

Seventy-two subjects had blood lead levels measured in the year prior to the measurement of blood pressure. Among these, we found no convincing evidence of an association between mean 1-year blood lead and blood pressure after controlling for the covariates as described above (diastolic model: blood lead (untransformed) regression coefficient $= 0.19$, $P = 0.16$; systolic model: blood lead (untransformed) regression coefficient $= 0.20$, $P = 0.44$). The results were similar using log-transformed lead exposure variables.

DISCUSSION

This study examined the relationship between long-term occupational lead exposure and several health

outcomes related to blood pressure. We found evidence of a small effect of lead on diastolic blood pressure, particularly for the cumulative measure of lead exposure. We found no convincing evidence of an association between lead exposure and other blood-pressure-related outcomes.

In interpreting our results, some important study limitations must be considered. One limitation is the lack of information about the temporal relationship between the exposure and the health outcome. Another potential concern is the problem of survivor bias due to deaths among the most severe cases (e.g., those with heart attacks and strokes). Among active employees and retirees who worked at the company for 10 or more years, however, only seven were known to have died. Similarly, a participation bias is possible if employees who left work due to poor health, including cardiovascular disease, were less likely to participate. Overall, the participation rate was low, and it was particularly low among retirees and employees on long-term disability. Data on nonparticipants, although incomplete, suggests a possible participation bias regarding treated hypertension, but not actual blood pressure. There was no evidence, however, of a meaningful difference between participants and nonparticipants with regard to level of lead exposure. Thus, it seems unlikely that our findings regarding the effects of lead are biased due to the selection of subjects. Another possible limitation is the small sample size of this study. Many of the studies (described below) that have found a relationship between blood lead and blood pressure or hypertension have been based on considerably larger samples and, thus, had greater power to detect a small effect.

The earliest evidence for an effect of lead exposure on blood pressure came from large, population-based surveys in the United States, Great Britain, Denmark, and Canada [Pocock et al., 1984; Harlan et al., 1985; Elwood et al., 1988; Neri et al., 1988; Grandjean et al., 1989]. These surveys generally found a small, but statistically significant, increase in blood pressure with increasing blood lead level. Similar results have been reported from studies of workers in occupations without significant workplace lead exposure. Although one study of government employees did not show any relationship between blood lead levels and blood pressure [Staessen et al., 1990], in most cross-sectional surveys of nonindustrial, occupational groups (bus drivers [Sharp et al., 1988], policemen [Weiss et al., 1986; Wolf et al., 1995], and government workers [Moreau et al., 1982]), a statistically significant, positive association between blood lead and blood pressure (systolic alone, diastolic alone, or both) has been observed. In other types of studies, a baseline blood lead has been associated with systolic pressure 4 years later, and lead body burden (tibia lead level) has been associated with hypertension [Hu et al., 1996]. Tibia lead levels have been shown to be correlated strongly with the cumulative blood lead measure used in our study [Somervaille et al., 1988].

The relationship between lead exposure and blood pressure also has been studied in workers in lead-exposed industries, including battery manufacturing. Concerns have been raised, however, about the validity and generalizability of the findings of many early studies due to problems in study methods [Hertz-Picciotto and Croft, 1993]. A relationship between blood lead and blood pressure has been found in some studies [Kirkby and Gyntelberg, 1985; de Kort et al., 1987; dos Santos et al., 1994], but not others [Cramér and Dahlberg, 1966; Lilis et al., 1982; Parkinson et al., 1987; Wu et al., 1996; Ehrlich et al., 1998]. In one longitudinal study, changes in blood lead seemingly were related to changes in diastolic pressure, but the association was not statistically significant [Neri et al., 1988]. The observation that the effect of lead on blood pressure is more pronounced at lower levels of lead exposure may explain the inconsistencies among occupational studies and between many occupational studies and the general population surveys [Goyer, 1993]; however, the differences may also be a result of sample size, choice of covariates, and types of exposure measurement. Unlike our study, which included a cumulative measure of lead exposure, the majority of occupational studies have looked at current blood lead level. As was the case when first noted in a 1993 review, the absence of a cohesive theory explaining how lead affects blood pressure makes it difficult to determine whether a recent or long-term exposure metric is the most relevant, although the data seem supportive of a chronic effect [Hertz-Picciotto and Croft, 1993].

We found evidence of a relationship between cumulative occupational lead exposure and diastolic blood pressure. Our cumulative exposure measure is the summation over time of the product of individual measurements of exposure and the duration of exposure at each level. The US Public Health Service has set a goal of keeping workers' blood lead levels below 25 μg/dl [PHS, 1991]. If a worker's blood lead level is 25 μg/dl for 30 years, the CBLI would be 750 μg/dl-yr, which is near the low end of the range of the highest tertile in our study. Recent data from laboratory-based surveillance systems in 27 states showed that each calendar quarter about 4,000 working-age adults are reported to have blood levels of 25 μg/dl or greater [Centers for Disease Control and Prevention, 1999].

Although we found evidence of a relationship between lead and diastolic blood pressure, we found no evidence of a relationship with systolic blood pressure and no convincing evidence of a relationship with hypertension. The inconsistency of these findings also is present in many of the previous studies of lead and blood pressure [Hertz-Picciotto and Croft, 1993]. For hypertension, our results varied with the cut-points used to classify subjects. While the choice of cut-points was made to follow convention regarding patient

management (140/90, [JNC, 1993]) or for consistency with other studies (160/95, [Hu et al., 1996]), a threshold value that separates hypertensives and normotensives does not exist. When using a more specific definition based on higher cut-points, we found a nonsignificant increasing risk of hypertension with cumulative lead exposure. Among published studies that have reported an analysis of hypertension as a dichotomous outcome, there is little consistency regarding the choice of cut-points and the finding of a lead–hypertension relationship; there are positive studies with both high and low cut-points, and negative studies with both high and low cut-points.

In this study, we had the opportunity to measure left ventricular mass by echocardiogram. Evidence for a relationship between left ventricular mass and lead exposure was found in one population-based survey, even after controlling for recognized cardiovascular risk factors [Schwartz,1991]. Our results (i.e., a non-statistically significant pattern of slightly increasing left ventricular mass with increasing occupational lead exposure) are not inconsistent.

ACKNOWLEDGMENTS

We gratefully acknowledge the dedicated assistance of a large survey team including Jenise Brassell, Christine Gersic, and Pat McGraw for microfilming medical and personnel records, Tammy Knight, Dave McElmurry, and Linda Wolf for echocardiography, Marian Coleman for reviewing microfilm and editing data, and Jenise Brassell, B.J. Haussler, Joe Hurrell, Michael McDonald, Elaine Moore, and Karen Worthington for questionnaires, anthropometry, and blood pressure. In addition, we thank Sherry Kopca from the battery plant for helping with the logistics and providing essential information, and the workers in the plant for their cooperation.

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