Environmental lead exposure does not increase blood pressure in the population: evidence from the Cadmibel Study

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Objective: Long-term exposure to high concentrations of lead may adversely affect several organ systems, but the possible influence of low-level lead exposure on blood pressure remains debatable. The present study examined this relationship in a cross-sectional population survey.

Methods: Blood pressure and lead exposure were measured in 1648 subjects (827 males and 821 females; mean age 45 years), drawn at random from the general population, but not being treated for hypertension.

Results: Systolic/diastolic blood pressure averaged 131/77 mmHg in the males and 124/74 mmHg in the females. Blood lead was higher in males than in females (0.5 versus 0.3 μmol/l, $P < 0.001$), but the opposite was observed for zinc protoporphyrin (1.0 versus 1.1 μg/g haemoglobin, $P < 0.001$). Total serum calcium was similar in both sexes (2.37 mmol/l). After adjustment for significant covariates (age, body mass index, pulse rate, serum creatinine and serum calcium, and for contraceptive pill intake and menopause in females), systolic pressure was negatively correlated with blood lead in men ($P < 0.05$); the partial correlations with blood lead were not significant for systolic pressure in females nor for diastolic pressure in either sex. After excluding males possibly exposed at work, the partial correlations between systolic and diastolic pressure and blood lead were negative ($P < 0.05$). Neither males nor females showed a significant relationship between blood pressure and the zinc protoporphyrin level in blood, an alternative index of lead exposure.

Conclusion: This study does not support the hypothesis that exposure to lead is associated with increased blood pressure in the population at large.

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Introduction

For more than 5000 years, in almost all parts of the world [1], lead has been part of the human environment [2]. Industry and the combustion of leaded fuel in car engines constitute the major present sources of lead emissions into the environment [2,3]. Lead enters the human body through inhalation of lead-containing particles present in the inspired air [4] and by the ingestion of contaminated foodstuffs [2,4–6] and drinking water [7–9]. Cigarette smoke [10,11] and alcoholic beverages [11,12] also contain lead but are avoidable. After entry into the human organism, lead is stored mainly in the bone [4,13]. Its half-life is estimated to be more than 5 years [13,14] but is characterized by a large interindividual variability [14].

Long-term exposure to high concentrations of lead may adversely affect the central and peripheral nervous system, the bone marrow, the kidney, the thyroid and the testes [15–17], but the possible effects of exposure to lead on blood pressure and on the prevalence and incidence of hypertension remains in dispute [8,11,12,18–36]. The morbidity associated with exposure of the general population to heavy metals was recently investigated in four Belgian districts with a wide range of exposure to cadmium. This cross-sectional survey, the Cadmium in Belgium (Cadmibel) Study [36–38], showed that exposure of the population to cadmium was not associated with an increased prevalence of hypertension and cardiovascular disease, although the risk of renal dysfunction was increased [17,38]. The Cadmibel Study [17,36–38] also offered an opportunity to explore the blood pressure effects of environmental exposure to lead, as evaluated from blood lead and zinc protoporphyrin in blood. In addition, the interaction between blood lead and serum calcium in the determination of blood pressure was investigated.

Subjects and methods

Subjects

The study protocol has been published in detail elsewhere [37]. A random population sample of 2327 subjects took part in the survey (age range 20–88 years). Subjects in this sample were excluded from the present analysis if not all relevant measurements were available (n = 251), if 24-h urine was judged to be under- or over-collected by previously published criteria [39] (n = 39), if the possibility of occupational exposure to heavy metals (n = 35) or of the subject being a smoker (n = 6) could not be ascertained from a self-administered questionnaire and if a subject was taking antihypertensive drugs (n = 348). With these exclusions, the present analysis included 1648 subjects, 827 males and 821 females.

Field work

On each of two separate home visits sitting blood pressure was measured five times consecutively by a trained observer [36], the pulse rate was counted over 1 min and body weight and height were determined. All subjects were thus characterized by the mean of 10 blood pressure readings and by two determinations of pulse rate, body weight and height. A self-administered questionnaire enquired into each participant's medical history, current and past occupations, smoking habits, consumption of alcohol and intake of drugs. All subjects collected a 24-h urine sample and underwent blood sampling within 2 weeks after the urine collection.

All observers were tested for the accuracy of their blood pressure measurements at 6-monthly intervals in two steps [37]. First, the observers recorded blood pressure readings from a film that showed a falling mercury column with Korotkoff sounds (*Measuring Blood Pressure*, production B-132; The Audio-Visual Centre, University of London, London, UK). Second, the observers were tested using live subjects and stethoscopes with double earpieces. The observers were considered to have passed the test when each of their pressure readings, for both the sound film and the measurements in live subjects, was within 5 mmHg of those taken by experienced medical staff.

Biochemical measurements

The biochemical techniques and procedures for quality control have been described elsewhere [37]. Lead was measured by electrothermal atomic absorption spectrometry [37] and serum zinc by flame atomic absorption spectrometry following deproteinization of the serum [40]. Serum total calcium was determined by compleximetric titration [41].

The biochemical determinations were performed by two laboratories. All tests were run in duplicate and certified reference standards were run along each series of samples. Ten per cent of the measurements of blood lead were performed in both laboratories. Assays were repeated if the difference between duplicate determinations in the same laboratory (precision) or the deviation from a given standard (accuracy) fell outside previously published limits [37], or if the results in a sample differed by more than 10% between the two laboratories [37]. For blood lead, the precision was required to be within 5% and the accuracy within 10%.

Statistical analysis

The SAS software package (SAS Institute Inc., Cary, North Carolina, USA) was used for statistical analysis. Where appropriate, a logarithmic transformation was used to normalize the distribution of the biochemical measurements.

The statistical methods included Student's t-tests and single and multiple linear regressions. Blood pressure was first plotted graphically by quintiles of the explanatory variables to evaluate the appropriateness of

linear correlation techniques. Significant covariates of blood pressure were then traced by stepwise regression. The relationships between blood pressure and blood lead and serum calcium were investigated with adjustments made for all variables identified as significant covariates. The age adjustments included both a linear and quadratic term.

Results

Characteristics of the participants

The present analysis included 827 males and 821 females. Their characteristics are summarized in Table 1. Mean ± SD age was 45± 15 years and the range was 20–88 years (Fig. 1). Thirty-two per cent (265) of the males reported possible exposure to heavy metals at work. Blood lead concentrations were higher in males than in females, but the opposite was observed for zinc protoporphyrin (Table 1).

Single correlations between blood pressure, blood lead and other covariates

The first-order correlations between blood pressure and various other measurements are shown in Table 2. In both males and females both systolic and diastolic blood pressure were positively correlated with advancing age (Fig. 1), body mass index, pulse rate and log γ-glutamyltranspeptidase, an index of alcohol intake.

In a single regression analysis, in which the correlation coefficients had not been adjusted for confounding factors, the correlation coefficient between systolic pressure and blood lead tended to be negative in males. In females, systolic and diastolic blood pressure were significantly and positively correlated with blood lead. Neither systolic nor diastolic pressure was significantly correlated with zinc protoporphyrin in either males or females. Systolic pressure in females was positively correlated with serum calcium.

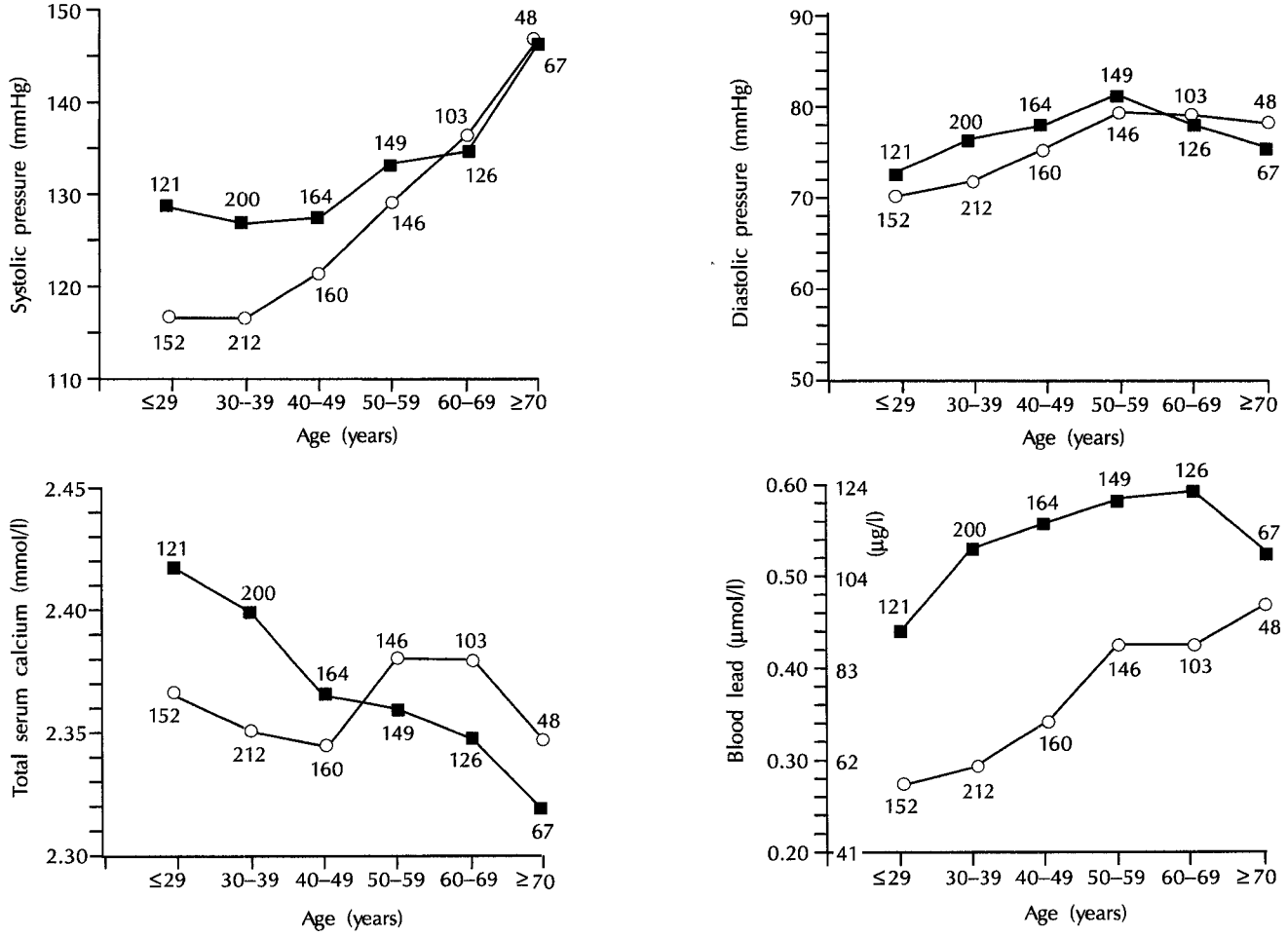

Fig. 1. Systolic and diastolic blood pressure, serum calcium and blood lead according to age and sex. (■, males; □, females). The number of subjects is indicated for all means.

Table 1. Characteristics of the study participants.

	Males (n = 827)	Females (n = 821)
Clinical measurements		
Age (years)	46± 15	44± 15
Body mass index (kg/m²)	25.3± 3.5	24.6± 4.8
Systolic pressure (mmHg)	131± 15	124± 16
Diastolic pressure (mmHg)	77± 9	74± 9
Pulse rate (beats/min)	74± 9	76± 7
Questionnaire		
Contraceptive pill (%)	–	23
Menopause (%)	–	44
Smokers (%)	49	38
Alcohol intake (%)	38	14
Occupational exposure (%)	32	3
Measurements in blood		
Lead (μmol/l)	0.5 (0.2–1.4)	0.3 (0.1–0.8)
γ- GT (U/l)	14 (4–49)	9 (2–32)
Protoporphyrin (μg/g)	1.0 (0.5–2.2)	1.1 (0.6–2.1)
Calcium (mmol/l)	2.37± 0.09	2.36± 0.09
Ferritin (μmol/l)	169 (32–906)	70 (12–392)
Creatinine (μmol/l)	108 (77–153)	91 (64–131)
Zinc (μmol/l)	13 (9–19)	12 (9–18)
Measurements in urine		
Volume (l/24 h)	1.65± 0.69	1.65± 0.75
Calcium (mmol/24 h)	5.00± 2.68	4.13± 2.19
Sodium (mmol/24 h)	193± 94	148± 72
Potassium (mmol/24 h)	71.1± 24.2	60.5± 20.7

Values are expressed as means± SD; the geometric mean and the 2-SD interval are given for logarithmically transformed variables. γ-GT, γ-glutamyltranspeptidase. Except for urinary volume, all sex differences were significant at the 5% probability level.

Table 2. Single correlation coefficients.

	Males (n = 827)		Females (n = 821)	
	SBP	DBP	SBP	DBP
Age	0.31 ($P< 0.001$)	0.15 ($P< 0.001$)	0.53 ($P< 0.001$)	0.36 ($P< 0.001$)
Body mass index	0.23 ($P< 0.001$)	0.32 ($P< 0.001$)	0.29 ($P< 0.001$)	0.35 ($P< 0.001$)
Pulse rate	0.15 ($P< 0.001$)	0.13 ($P< 0.001$)	0.10 ($P=0.004$)	0.07 ($P=0.06$)
Log blood lead	−0.05 ($P=0.14$)	0.04 ($P=0.16$)	0.23 ($P< 0.001$)	0.15 ($P< 0.001$)
Log protoporphyrin	0.04 ($P=0.29$)	0.03 ($P=0.32$)	0.07 ($P=0.04$)	0.05 ($P=0.16$)
Log γ-GT	0.08 ($P=0.02$)	0.22 ($P< 0.001$)	0.22 ($P< 0.001$)	0.21 ($P< 0.001$)
Serum calcium	0.01 ($P=0.87$)	0.03 ($P=0.35$)	0.09 ($P=0.006$)	0.07 ($P=0.05$)
Log serum ferritin	0.07 ($P=0.07$)	0.10 ($P< 0.001$)	0.18 ($P< 0.001$)	0.11 ($P< 0.001$)
Log serum creatinine	0.24 ($P< 0.001$)	0.08 ($P=0.01$)	0.10 ($P=0.01$)	0.05 ($P=0.16$)
Log serum zinc	−0.04 ($P=0.29$)	0.05 ($P=0.14$)	0.01 ($P=0.75$)	−0.01 ($P=0.91$)
Urinary calcium	−0.02 ($P=0.64$)	0.06 ($P=0.07$)	0.01 ($P=0.95$)	0.04 ($P=0.31$)
Urinary sodium	0.03 ($P=0.38$)	−0.00 ($P=0.89$)	−0.06 ($P=0.11$)	−0.03 ($P=0.33$)
Urinary potassium	−0.05 ($P=0.13$)	−0.04 ($P=0.28$)	−0.05 ($P=0.13$)	0.02 ($P=0.59$)

SBP, DBP, systolic, diastolic pressure; γ-GT, γ-glutamyltranspeptidase.

Covariates of blood pressure

The stepwise multiple regression showed that a large part of the blood pressure variance was explained by age (linear and squared terms combined). The multiple partial correlation coefficients for the age effect ranged from 0.22 to 0.49 and the partial correlation coefficient for body mass index from 0.19 to 0.27 (Table 3). The other significant blood pressure covariates were pulse rate (partial correlation coefficient 0.12–0.16), serum calcium (0.05–0.13) and serum γ-glutamyltranspeptidase (0.06–0.13). Serum ferritin made no contribution to the explanation of blood pressure variance, in either males or females.

Lead as an independent determinant of blood pressure

In a free-running stepwise regression procedure, systolic pressure in the males was negatively and independently correlated with blood lead (partial $r = -0.07$; $P = 0.04$). The regression coefficient was compatible with a 1.5-mmHg decrease in the systolic pressure for a doubling of the blood lead concentration (Table 3, Fig. 2). If males with a possible exposure to heavy metals at work were excluded from the analysis, the slope of systolic pressure on blood lead did not change materially (−9.8± 3.4 mmHg per log μmol/l; $P = 0.004$); furthermore, with this exclusion, diastolic pressure was also negatively correlated with blood lead (−4.8± 2.2 mmHg per log μmol/l; $P = 0.03$). In a free-running stepwise regression procedure without a lead–calcium interaction term, blood lead was not identified as a significant covariate of blood pressure in females.

Zinc protoporphyrin was not a significant determinant of blood pressure, either in males or females, according to our regression model.

The lead–calcium interaction

In a further step in the analysis, we calculated the percentage contribution made by blood lead, serum calcium and the interaction between log blood lead and serum calcium to the blood pressure variance. In males, whether those possibly exposed to heavy metals at work were excluded or not, there was no evidence of a significant interaction between log blood lead and serum calcium.

In females, both main effects, i.e. blood lead and serum calcium and the interaction term, were significantly correlated with blood pressure (Table 4, Fig. 3). The regression coefficients were compatible with a 1.0-mmHg decrease in systolic pressure for a doubling of the blood lead concentration at a serum calcium level of 2.31 mmol/l (25th percentile). By contrast, at a serum calcium concentration of 2.42 mmol/l (75th percentile), a doubling in blood lead was associated with a 1.5-mmHg increase in systolic pressure.

Table 3. Covariates of blood pressure in a stepwise multiple regression.

	Males (n = 827)		Females (n = 821)	
	SBP	DBP	SBP	DBP
R^2	0.23	0.20	0.36	0.24
Intercept	32± 19	31± 4	57± 14	36± 4
Partial regression coefficients				
Log blood lead	−5.2± 2.4*	−1.1± 1.6	0.5± 2.8	−0.3± 1.7
Age (linear)	−0.8± 0.2***	0.7± 0.1***	−0.5± 0.2**	0.7± 0.1***
Age (squared)	+0.012± 0.002***	−0.007± 0.001***	+0.007± 0.001***	+0.005± 0.001***
Body mass index	0.9± 0.1***	0.71± 0.09***	0.6± 0.1***	0.46± 0.06***
Pulse rate	0.21± 0.05***	0.13± 0.03***	0.23± 0.05***	0.11± 0.03***
Log γ-GT	3.2± 1.8*	4.1± 1.2***	4.1± 1.8*	2.1± 1.1*
Serum calcium	13± 5**	NS	13± 5*	NS
Log serum creatinine	17± 6**	NS	NS	NS
Urinary potassium	NS	−0.04± 0.01***	NS	NS
Smoking	NS	−1.8± 0.6***	NS	NS
Alcohol intake	NS	NS	NS	2.1± 0.8**
Contraceptive pill	–	–	NS	NS
Menopause	–	–	NS	2.6± 0.7***

Values are expressed as means± SEM. SBP, DBP, systolic, diastolic blood pressure; γ-GT, γ-glutamyltranspeptidase. Smoking, alcohol, contraceptive pill, menopause, all coded 0 when condition absent and 1 if present. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Contraceptive SBP: t value for entering, 1.6 ($P = 0.12$); contraceptive DBP: t value for entering, 1.3 ($P = 0.18$); menopause SBP: t value for entering, 1.2 ($P = 0.23$).

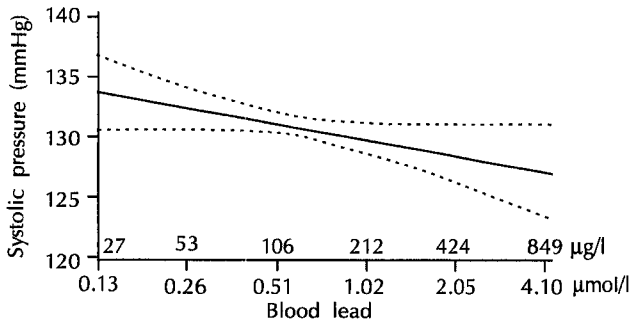

Fig. 2. Relationship between systolic pressure and blood lead in males (n = 827) after adjustment for significant covariates. Broken lines show the 95% confidence interval.

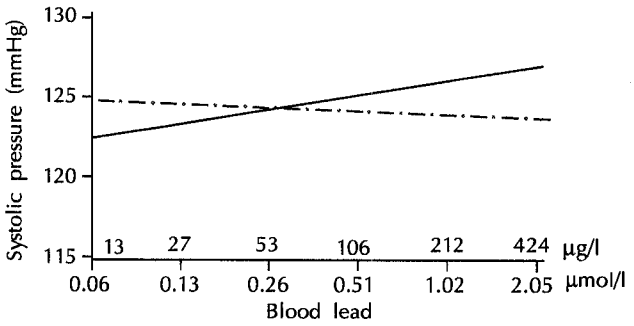

Fig. 3. Relationship between systolic pressure and blood lead in females (n = 821), after adjustment for significant covariates, for two different serum calcium levels (— - —, 2.31 mmol/l, representing the 25th percentile of the distribution; ——, 2.42 mmol/l, representing the 75th percentile).

Table 4. Blood lead, serum calcium and the lead–blood pressure interaction as determinants of systolic pressure in females.

R^2 (for all covariates)	0.37	
Intercept	−26± 32	
Partial regression coefficients± SEM		
Log blood lead	−179± 63	($P = 0.005$)
Serum calcium	48± 14	($P < 0.001$)
Lead–calcium interaction	76± 27	($P = 0.005$)

Covariates included age (linear and squared term), body mass index, pulse rate and log γ-glutamyltranspeptidase.

Discussion

The Cadmibel Study offered a framework for exploring the influence of blood lead on blood pressure in the population at large. Subjects treated with antihypertensive drugs were excluded from the present analysis, because no measurements of the true untreated blood pressure were available. After adjustment for significant covariates, systolic pressure in men was independently and negatively correlated with blood lead. In addition, blood pressure was not correlated with zinc protoporphyrin, an alternative index of lead exposure, in either males or females. Thus, the present study does not support the hypothesis that low-level lead exposure would lead to an increase in blood pressure in the population at large.

Several reports of a possible association between lead exposure and blood pressure have been published, but do not reflect a consensus among scientists [8,11,12,18–36]. After adjustment for significant covariates, a significant and positive relationship between blood pressure and blood lead has been reported in some studies [18–33] but other studies failed to find a relationship [11,12,34–36].

In the second National Health and Nutrition Examination Survey (NHANES II) in the United States, 20 322 people aged from 6 months to 74 years were examined, and blood lead was determined in 9932 subjects

[18,21,26,30,32]. The results showed that systolic and diastolic pressures, adjusted for their main covariates, were positively correlated with blood lead in white and black males, but not in white and black females [21]. The standardized regression coefficients showed that in males the association between blood pressure and blood lead was about five times less important than the correlations between blood pressure and age and body mass index. However, no standard deviations for systolic and diastolic pressures were presented in the main NHANES II report [21], so that the dose–response relationship between blood pressure and blood lead was difficult to estimate from that paper [21].

In a later re-analysis of the NHANES II data [26], a forward stepwise regression was used to investigate the independent correlation between blood pressure and blood lead for 26 age intervals of 20 years each, ranging from 21–40 years through to 46–65 years. Overall, a doubling of the blood lead concentration was associated with a blood pressure increase of 1.1 mmHg systolic and 1.4 mmHg diastolic. However, the analyses were also carried out separately in white males, in white females, and in blacks of either sex. These calculations showed that the correlations between blood pressure and blood lead in the NHANES II database lacked consistency and reliability across the various race, sex and age groups [26]. Moreover, in the NHANES II study, only two blood pressure readings per visit were obtained in each subject [30,42], whereas in the present study each subject was visited twice and was characterized by the average of 10 readings.

The observers collaborating in the present project were tested for the accuracy of their blood pressure readings at 6-monthly intervals [37]. All blood pressure readings were obtained in a relaxed home environment after the subjects had rested for 5 min in the sitting position. In most other studies, fewer blood pressure readings have been obtained, often at special clinics, and details on the conditions of the blood pressure measurement have not always been reported. These differences in methodology could at least partly explain why divergent results have been reported with respect to the possible relationship between blood pressure and lead exposure.

The white coat effect, i.e. a transient rise in blood pressure in response to the observer, is increasingly recognized as an important problem in daily clinical practice [42,43]. Ambulatory blood pressure measurement is believed to minimize the white coat effect and to increase the reproducibility of the blood pressure readings [44]. Further information on the lead–hypertension issue may be obtained by studies that use ambulatory blood pressure monitoring to assess blood pressure and an X-ray fluorescence technique [45] to determine the bone lead content as an index of lifetime lead exposure. Indeed, over 95% of the lead body burden is stored in bone tissue [2,13] where the half-life of lead is estimated to vary from 2 to 27 years [13,14].

In the present study the exposure to lead was assessed not only from blood lead, but also from the zinc protoporphyrin level in blood. It has been hypothesized that zinc protoporphyrin may reflect the lead burden on target organs, such as the kidney and the central nervous system [46]. Nevertheless, in the present analysis, the correlations between blood pressure and zinc protoporphyrin in blood were not significant. This may indicate that the relationship between blood pressure and blood lead is spurious or is a result of unknown confounding factors.

In females with a high serum calcium a doubling in the blood lead concentration was associated with a 1.5-mmHg increase in systolic pressure. By contrast, in females with low serum calcium levels, a doubling in blood lead was associated with a 1.0-mmHg decrease in systolic pressure (Fig. 3).

At present, there is no known explanation for this interaction between lead and calcium. One possibility is that lead, a divalent cation, competes with calcium at various target sites, such as calcium channels in vascular smooth muscle cells or sites required by the mechanisms regulating intracellular calcium and cell energy metabolism [47]. Divergent lead effects, depending on the extracellular calcium concentration, have previously been observed in isolated rat heart preparations [48]. The presence of lead at 30 µmol/l in the perfusion fluid induced cardiotoxic manifestations similar to those reported for lead poisoning *in vivo*, but when the calcium level in the perfusion fluid was reduced from 5.0 to 3.5 mmol/l these cardiotoxic effects were antagonized [48].

In conclusion, the present study does not support the hypothesis that exposure to lead would lead to increased blood pressure in the population at large.

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