

META-ANALYSIS

Hypertension caused by low-level lead exposure: myth or fact?

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Background: Several reports on the possible association between low-level lead exposure and blood pressure reflect diverging views. This meta-analysis aimed to find a common denominator in the published literature and to estimate whether a relationship exists between blood pressure and levels of lead in the blood.

Methods: Of the studies reviewed, 23 provided sufficient details to be considered. The meta-analysis included 33 groups with a total of 33 141 subjects, who had been recruited from the general population in 13 surveys and from occupational groups in 10 studies. In all but four studies the results were adjusted for age, and most studies took into account additional confounding factors.

Results: The association between blood pressure and blood lead was similar in both men and women. In the combined studies, a twofold increase in blood lead concentration was associated with a 1.0 mmHg rise in systolic pressure (confidence interval 0.4–1.6 mmHg; $P=0.002$) and with a 0.6 mmHg increase in diastolic pressure (confidence interval 0.2–1.0 mmHg; $P=0.02$). The association with systolic pressure strongly relied on the inclusion of a large study ($n=3851$) in which women's blood pressure was measured at the end of pregnancy. The association with diastolic pressure was largely due to a population survey in the USA ($n=6289$). There was no relationship across studies between the strength of the blood pressure–blood lead relationship and the mean blood lead concentration.

Conclusion: The published evidence suggests that there can only be a weak positive association between blood pressure and lead exposure. Any such relationship may not be causal and is unlikely to entail any public-health implication in terms of hypertension-related complications. Nevertheless, these assumptions need to be confirmed in prospective population studies.

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Introduction

Lead accumulates in the human body and has been implicated in the pathogenesis of renal dysfunction [1,2] and hypertension [3,4], particularly among industrial workers who are heavily exposed to lead [5–8] and in alcoholics drinking 'moonshine' whisky [9,10]. As a consequence of industrialization and motorized traffic, populations as a whole are now being exposed to lead pollution, albeit in much lower concentrations than industrial workers in the past. It has been suggested, however, that exposure to even lower levels of lead than these may lead to substantial excess morbidity [11], although in individuals the relative risk may be extremely small and barely detectable.

One of the main ways in which low-level lead exposure might have an adverse effect on public health is through its association with hypertension. Plausible pathophysiological mechanisms have been described [4,12,13], but the reports dealing with the positive association between lead exposure and blood pressure are not universally accepted [14]. The objectives of this meta-analysis were to determine whether the available data support a positive association and how strong such a relationship between blood pressure and lead exposure may be.

Methods

General design

First, relevant studies were identified. In accordance with current guidelines [15,16], the criteria determining the eligibility of a study were established before the statistical analysis took place. The effect of lead exposure on blood pressure and its standard error were then identified for each group of subjects appearing in the individual studies. In this article, preference was given to the term 'association size' instead of 'effect size' because the causality of the association between blood pressure and low-level lead exposure has not yet been conclusively established. Second, the estimates of the association sizes from the individual studies were expressed on a common scale in order to make the calculation of a pooled association size possible. However, before pooling was undertaken, it was important to determine whether the studies could reasonably be described as sharing a common association size [15,16]. This was formally explored using a statistical test of homogeneity. A pooled association size and corresponding *P* values were then computed, combining the evidence from all studies both with and without weighting by the size of the groups included in the analysis. Finally, a sensitivity analysis was performed to ensure that the pooled results were not critically dependent on only one or a few studies.

Data collection

Articles on the association between blood pressure and lead exposure were identified from computer searches

of the English, French and German literature from January 1980 to October 1993 using the Medical Literature Analysis and Retrieval System (MEDLARS), existing compilations of the literature [4,17] and presentations at international meetings. Studies were eligible for inclusion in this meta-analysis if at least 50 people had been recruited, if the minimum age of the participants was 10 years or higher and if both blood pressure and blood lead had been measured and presented with sufficient detail to estimate or calculate the size of the association.

Within any one study, preference was given to blood pressure results adjusted for age and body mass index and additional factors of proven importance. Whenever possible, subjects were divided into separate groups according to sex and race.

Estimation of the association size

The association size was estimated for each group as the blood pressure change that would be associated with a doubling of the blood lead concentration. For reports in which blood lead was expressed on a linear scale, the association size was calculated assuming a twofold increase of the mean blood lead concentration. For studies in which the association size was expressed on a logarithmic scale, the change in blood pressure associated with a doubling of the blood lead concentration was calculated by multiplying the regression coefficient by 0.30 if common logarithms had been used and by 0.69 for natural logarithms.

The standard error of the blood pressure difference associated with a given change in the blood lead concentration was not reported in all studies. In these instances, the standard error was estimated from the published association size and the test statistic corresponding with the reported *P* value. If the parameters of a non-significant blood pressure effect were not reported, the authors of the paper were contacted in order to avoid bias resulting from the exclusion of non-significant studies, an important problem in any meta-analysis [18]. If no additional information was made available, the non-significant effects were assumed to be zero and the non-significant *P* values to be 0.50, according to the suggestion of Needleman and Gatsonis [19]. Summary statistics were then calculated both with and without the studies for which these assumptions had to be made.

Statistical analysis

Statistical analyses were performed using SAS software (The SAS Institute Inc., Cary, North Carolina, USA). Regression equations across studies and the computation of the overall association size were weighted by the number of subjects included in each single group.

Joint *P* values were calculated using two different techniques: Stouffer's method, as modified by Mosteller and Bush, and Fisher's approach [15]. In Fisher's procedure, the logarithm of the product of the individual *P* values was multiplied by -2 . The resulting quantity follows a chi-square distribution with $2k$ degrees of freedom, where k refers to the number of pooled groups. Fisher's

procedure was not weighted because weighting may produce computational instability [15]. Stouffer's procedure involved transforming each *P* value to its corresponding normal score and then averaging these *z*-scores, using degrees of freedom (number of subjects - 1) as weights. The weighted *z*-score average was employed to construct one-sided 95% confidence intervals (CIs) for the pooled association size. As a test of homogeneity, the *z*-scores of the individual studies were ranked and plotted to see whether they were on a straight line.

Results

Selection of studies

Of the studies reviewed [5,6,9-11,14,20-67], 13 reports were excluded. One study reported only on young children (age range 1-3 years) [22], one was a case report [10], one recruited fewer than 50 people [9], four estimated exposure from measurements other than those

of blood lead concentration [23-25,27] and six did not provide enough information to compute the association size [5,6,20,21,26,28]. Two of the latter studies [20,21] were based on a comparison of the blood lead levels in hypertensive and normotensive subjects.

Characteristics of the selected studies

The 23 studies included in the meta-analysis are listed in chronological order (year of main publication) in Table 1. Of these, 13 recruited participants from the general population, four included employees with clerical jobs and six included blue-collar workers. In 18 cross-sectional studies, the possible influence of lead exposure was investigated by carrying out a regression analysis between blood pressure and blood lead levels. In three studies [40,55,56], blood pressure was measured in exposed and control groups with differing blood lead levels. The longitudinal Boston [36,37] and Glostrup [60] studies applied autoregression to investigate the correlation between lead at baseline and blood pressure during follow-up.

Table 1. Characteristics of the study population.

Reference	n	Subjects	Men (%)	HT	Age in years (range)	SBP	DBP	Lead (μmol/l)	QC	Scale	Information
Pocock <i>et al.</i> [14,29,30]	7379	GP	100	Yes	49 (40-59)	145	82	0.73 (0.10-3.20) ^{Ae}	BP, L	log	S, C, R
Kromhout <i>et al.</i> [31,32]	152	GP	100	Yes	67 (57-76)	154	92	0.88 (0.52-1.35) ^{Ac}	BP, L	Lin	0
Orssaud <i>et al.</i> [33-35]	431	WC	100	Yes	41 (24-55)	131	75	0.88 (0.43-2.41) ^{Ae}	BP	Lin	S, C, R
Weiss <i>et al.</i> [36,37]	89	WC	100	Yes	47 (30-64)	122	83	1.18 (<0.9->1.4) ^{Mx}	BP	Lin (D)	0
de Kort <i>et al.</i> [38,39]	105	BC	100	No	40 (25-80)	136	83	1.41 (0.21-4.02) ^{Ae}	BP	Lin	S, C, R
Lockett and Arbuckle [40]	116	BC	100	Yes	32 (?-?)	119	80	1.81 (0.72-4.61) ^{Ae}	ND	Lin (G)	0
Parkinson <i>et al.</i> [41]	428	BC	100	Yes	36 (18-60)	127	80	1.35 (0.29-2.39) ^{Ac}	BP	Lin	0
Rabinowitz <i>et al.</i> [42]	3851	GP	0	Yes	28 (18-38)	121	76	0.34 (0.18-0.49) ^{Ac}	BP-0	In	S, R
Elwood <i>et al.</i> [43-45] ¹	1136	GP	100	Yes	56 (49-65)	146	87	0.61 (0.29-1.26) ^{Gc}	BP	log	0
Elwood <i>et al.</i> [44,45] ²	1721	GP	50	Yes	41 (18-64)	127	78	0.49 (0.22-1.12) ^{Gc}	BP	log	0
Gartside <i>et al.</i> [11,46-49] ³	6289	GP	53	Yes	30 (10-74)	127	80	0.65 (0.10-4.63) ^{Ge}	BP, L	log	S, C, R
Neri <i>et al.</i> [50] ⁴	288	BC	100	?	?(?-?)	?	?	2.18 (0.29-3.14) ^{Ae}	ND	Lin	S
Neri <i>et al.</i> [50] ⁵	2193	GP	?	Yes	45 (25-65)	?	?	1.13 (0.00-2.27) ^{Me}	ND	Lin	NA
Sharp <i>et al.</i> [51-53]	288	WC	91	No	42 (28-64)	126	81	0.31 (0.10-0.72) ^{Pe}	BP, L	In	0
Grandjean <i>et al.</i> [54,60] ⁶	1050	GP	48	Yes	40 (40-40)	?	?	0.56 (0.19-2.90) ^{Ae}	BP, L	In	0
Reimer and Tittelbach [55]	58	BC	100	?	32 (?-?)	134	81	1.93 (0.62-3.39) ^{Ac}	ND	Lin (G)	0
Apostoli <i>et al.</i> [56,57]	525	GP	48	Yes	45 (21-60)	132	84	0.63 (0.10-1.36) ^{Ae}	BP	Lin	S, C, R
Morris <i>et al.</i> [58]	251	GP	58	Yes	?(23-79)	?	?	0.36 (0.24-1.88) ^{Ae}	BP	In	NA
Staessen <i>et al.</i> [59] ⁷	531	WC	75	Yes	48 (37-58)	126	78	0.55 (0.20-1.70) ^{Ge}	BP, L	log	0
Møller <i>et al.</i> [54,60] ⁸	439	GP	100	Yes	40 (40-40)	?	?	0.66 (0.24-2.90) ^{Ae}	BP, L	In	0
Hense <i>et al.</i> [61]	3364	GP	51	Yes	48 (28-67)	129	80	0.38 (0.06-1.79) ^{Ae}	BP, L	Lin	S, C, R
Maheswaran <i>et al.</i> [62]	809	BC	100	Yes	43 (20-65)	129	84	0.62 (0.00-4.73) ^{Ae}	BP	Lin	S, C, R
Staessen <i>et al.</i> [63-67] ⁹	1648	GP	50	Yes	45 (20-88)	127	76	0.44 (0.08-3.50) ^{Ge}	BP, L	log	0

GP, sample from general population; BC, blue collar workers; WC, white collar employees; HT, hypertensive patients; SBP, mean systolic blood pressure; DBP, mean diastolic blood pressure; Lead, measure of central tendency; A, arithmetic mean; G, geometric mean; P, P₅₀(median); M, midpoint of range. The spread of blood lead is given between parentheses: e, extremes; c, P₅-P₉₅ interval, P₁₀-P₉₀ interval or interval equal to four times the standard deviation; x, approximate limits of distribution. QC, Quality control; BP, well standardized blood pressure measurements; L, quality control programme for the blood lead determinations was mentioned; BP-0, blood pressure readings not standardized; ND, published articles provided no details on standardization of blood pressure measurements nor on quality control of the lead determinations; Scale, the scale on which blood lead was expressed to compute the association size; Lin, linear; log, common logarithm; In, natural logarithm. (G) indicates that the blood pressure was compared between groups with low and high exposure to lead and (D) that groups were contrasted in a regression model with use of dummy variables. 0, no information requested; NA, information requested but no longer available; S, descriptive statistics; C, single (unadjusted) correlations; R, multiple linear regression equations. Where available, the information provided by the authors was used rather than the often incomplete published data. ¹Caerphilly Study; ²Welsh Heart Program; ³NHANES II Survey (additional information was requested from Dr J. Schwartz, Environmental Protection Agency, USA and from Dr P.S. Gartside, University of Cincinnati, USA, but could only be obtained from the latter source); ⁴foundry workers; ⁵Canadian Health Survey; ⁶Glostrup Population Study, cross-sectional analysis (1976); ⁷London Civil Servants; ⁸Glostrup Population Study, longitudinal analysis (1976-1987); ⁹Cadmibel Population Study.

The blood lead concentration was expressed on a linear scale in 12 studies and on a logarithmic scale in 11. Only four studies [40,44,55,56] looked at the association between blood pressure and blood lead without any adjustment for possible confounding factors. In all but five reports [40,44,54–56], the results were adjusted for age, although in one [54] the subjects were of the same age. Body mass index or body weight were entered into the multivariate models of 17 studies [29,31,34,36,41,42,47,50 (which includes two studies),51,54,56,59,60–62,67]. Most studies also con-

sidered additional confounding variables, such as smoking [36,41,42,47,54,56,59,60,62,67], alcohol consumption [29,34,36,41,47,54,56,59–62,67], caffeine intake [51], dietary calcium intake or serum calcium [58,59,67], serum zinc [50], exposure to cadmium [38,67], blood haemoglobin concentration [50,54] or haematocrit readings [42,61], physical activity or fitness [54,60] and socioeconomic status [29,41,47].

The 23 studies listed in Table 1 included 33 different groups of subjects. Of the 23, 21 studied only men, 10

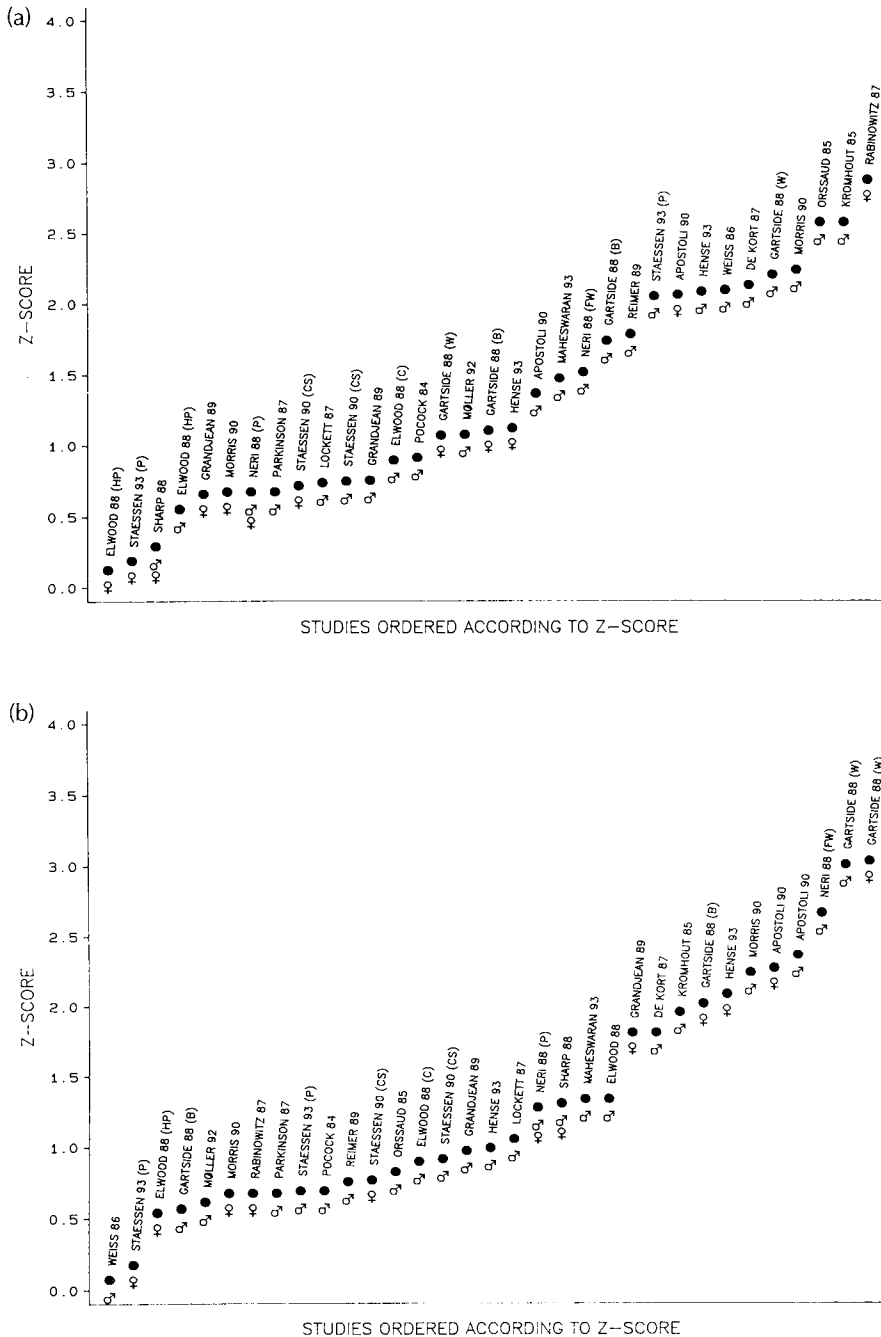


Fig. 1. The z-scores for the association between systolic (a) and diastolic (b) pressure and blood lead in 33 groups. For each group, the following details are given: sex, first author, year of publication and certain additional characteristics. C, Caerphilly study [43–45]; HP, Welsh Heart Program [44,45]; W, whites [46–49]; B, blacks [46–49]; FW, foundry workers [50]; CS, civil servants [59]; P, population study [63–67]. The ordered z-scores represented a continuum with no evidence for a bimodal or other distribution, confirming the hypothesis of homogeneity.

only women and two both men and women. In total, the studies involved 33 141 subjects. The association sizes for each of the groups involved in the meta-analysis were obtained for systolic (Fig. 1a) and diastolic (Fig. 1b) blood pressure from the published articles or directly from the authors for nine studies (Table 1).

Summary statistics

The z-scores for all the groups included in the meta-analysis represented a continuum with no evidence for a bimodal or other distribution (Fig. 2). Thus, the hypothesis of homogeneity was not rejected.

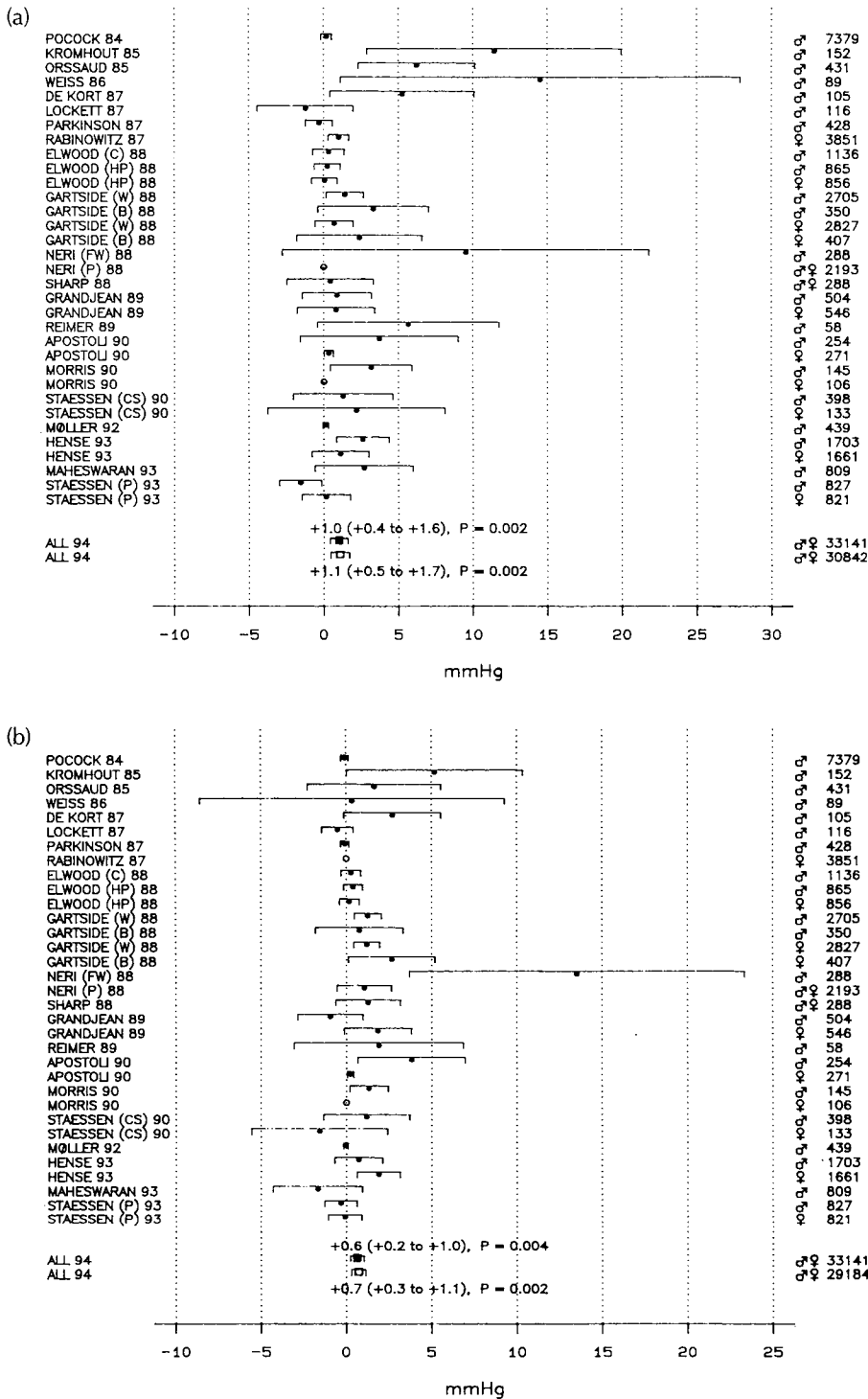


Fig. 2. Differences in the systolic (a) and diastolic (b) pressure (point estimate with 95% confidence interval) associated with a doubling of blood lead concentration. Closed circles represent individual groups and squares the pooled association sizes. For each group, the following details are given: sex, first author, year of publication, certain additional characteristics (C, Caerphilly study [43–45]; HP, Welsh Heart Program [44,45]; W, whites [46–49]; B, blacks [46–49]; FW, foundry workers [50]; CS, civil servants [59]; P, population study [63–67]) and the number of subjects. ○, groups for whom a non-significant systolic [50,58] or diastolic [42,58] association size was assumed to be zero. □, overall association size after removal of the latter subgroups.

The pooled *P* values obtained using Fisher's method and Stouffer's approach are shown combined for both sexes and separately in Table 2. The analyses initially included all available data. The results in men and women were identical. For all groups and both sexes combined, a twofold increase of blood lead concentration was associated with a 1.0 mmHg increase in systolic pressure (95% CI +0.4 to +1.6 mmHg; *P*=0.002), and with a 0.6 mmHg rise in diastolic pressure (95% CI +0.2 to +1.0 mmHg; *P*=0.004).

At a further stage of the analysis, subgroups of patients for whom the association size was reported as non-significant but for whom details of the statistical parameters were not available were excluded. This excluded two studies on systolic pressure [50,58] and two on diastolic pressure [42,58] in women. In this analysis, a doubling of blood lead concentration was associated with an increase in systolic pressure of 1.1 mmHg (95% CI +0.5 to +1.7 mmHg; *P*=0.002), and with a rise in the diastolic pressure of +0.7 mmHg (95% CI +0.3 to +1.1 mmHg; *P*=0.002).

Sensitivity analysis

The sensitivity of the findings was examined by removing one study at a time from the analysis and recalculating the joint *P* values using Stouffer's method. For systolic pressure, the overall statistical significance was largely determined by a study in women in the final stages of pregnancy [42] (Fig. 3). When the latter study was excluded, the pooled *P* value dropped to 0.02 and the 95% CI of the association size for systolic pressure ranged from +0.2 to +1.9 mmHg. Conversely, when a large negative study in men [29,30] was excluded, the association size rose to a 1.3 mmHg increase in systolic pressure associated with a doubling of the lead blood concentration (95% CI +0.7 to +1.8 mmHg; *P*<0.001).

The significant overall result for diastolic pressure was heavily dependent on the inclusion in the analysis of the National Health and Nutrition Examination Survey (NHANES)-II results [11,46-49] in white but not black subjects (Fig. 3). The exclusion of white men or women from the meta-analysis broadened the 95% CI of the association size for diastolic pressure so that it ranged from +0.2 to +1.8 (*P*=0.02) and from +0.1 to +1.9 mmHg (*P*=0.03), respectively.

In the 25 groups in which the average blood lead concentration was less than 1 µmol/l (*n*=29055), the association size averaged +0.9 mmHg (CI +0.4 to +1.5 mmHg; *P*=0.007) for systolic pressure and +0.6 mmHg (CI +0.2 to +0.9 mmHg; *P*=0.009) for diastolic pressure. In the eight other groups (*n*=4086), in which the mean blood lead concentration was 1 µmol/l or higher, the association sizes tended to be larger, but were not statistically significant. They averaged +1.7 mmHg (CI -2.3 to +5.7 mmHg; *P*=0.25) for systolic pressure and +1.3 mmHg for diastolic pressure (CI -0.6 to +3.1 mmHg; *P*=0.08). Overall there was no relationship across the 33 groups between the association size and the mean blood lead concentration (Fig. 4); the weighted correlation coefficients were only 0.0001 (*P*=0.98) for systolic pressure and 0.10 (*P*=0.57) for diastolic pressure.

In the 19 groups where the relationship between blood pressure and blood lead was studied on a logarithmic scale (*n*=24583), the association size averaged +0.9 mmHg (CI +0.2 to +1.6 mmHg; *P*=0.02) for systolic pressure and +0.5 mmHg (CI +0.1 to +0.9 mmHg; *P*=0.03) for diastolic pressure. In the 14 other groups (*n*=8558), in which the association was studied on a linear scale, the association sizes averaged +4.4 mmHg (+1.2 to +7.6 mmHg; *P*=0.01) for systolic pressure and

Table 2. Pooled *P* values and overall association sizes between blood pressure and blood lead.

		<i>n</i>	χ^2	Z-score	Association size
Both sexes*					
All studies	SBP	33 141	127 (<0.001)	2.8 (=0.002)	+1.0 (+0.4 to +1.6)
	DBP	33 141	126 (<0.001)	2.6 (=0.004)	+0.5 (+0.2 to +1.0)
Selected studies†	SBP	30 842	124 (<0.001)	2.9 (=0.002)	+1.1 (+0.5 to +1.7)
	DBP	29 184	124 (<0.001)	2.9 (=0.002)	+0.7 (+0.3 to +1.1)
Men					
All studies	SBP	19 181	95 (<0.001)	2.0 (=0.021)	+1.2 (+0.2 to +2.2)
	DBP	19 181	76 (<0.001)	1.5 (=0.064)	+0.5 (-0.1 to +1.1)
Women					
All studies	SBP	11 479	30 (=0.067)	2.2 (=0.013)	+0.8 (+0.2 to +1.5)
	DBP	11 479	43 (=0.002)	2.3 (=0.012)	+0.7 (+0.2 to +1.3)
Selected studies†	SBP	11 373	30 (=0.067)	2.2 (=0.013)	+0.9 (+0.2 to +1.5)
	DBP	7 522	43 (<0.007)	2.3 (=0.012)	+1.1 (+0.3 to +1.9)

χ^2 , statistic derived by Fisher's method with unweighted *P* value in parentheses [15]. Z-score, statistic devised by Stouffer's method with one-sided *P* value in parentheses [15]. The pooled z-scores were weighted by the number of subjects in each group. Association size, differences in the blood pressure associated with a twofold increase in the blood lead concentration (with 95% confidence interval between parentheses). SBP, systolic blood pressure; DBP, diastolic blood pressure. *Includes two studies [50,51] in which the effects in men and women were not separately reported. †Excludes studies for which the association size was assumed to be zero and the *P* value to be 0.5 (see Methods for further details).

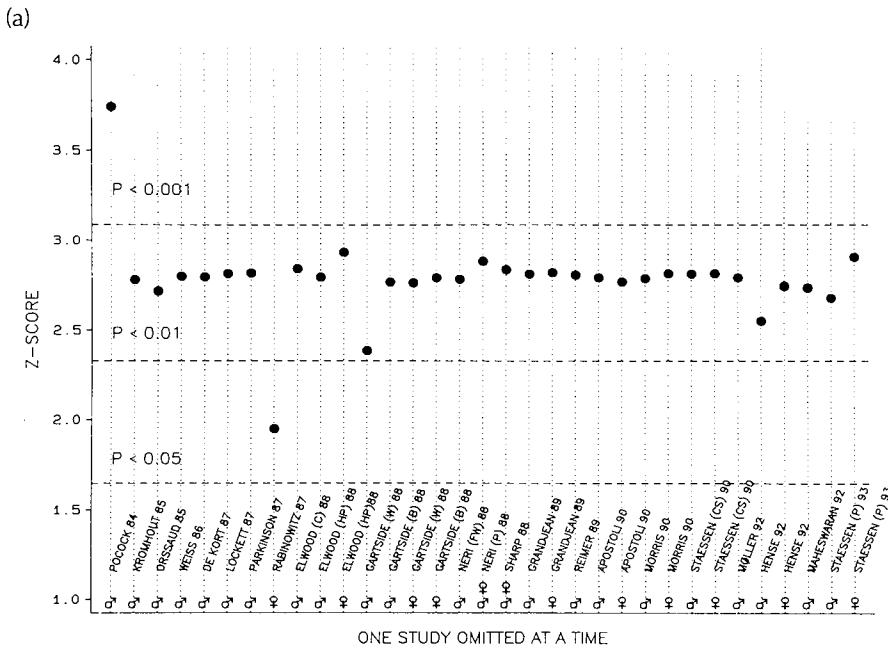
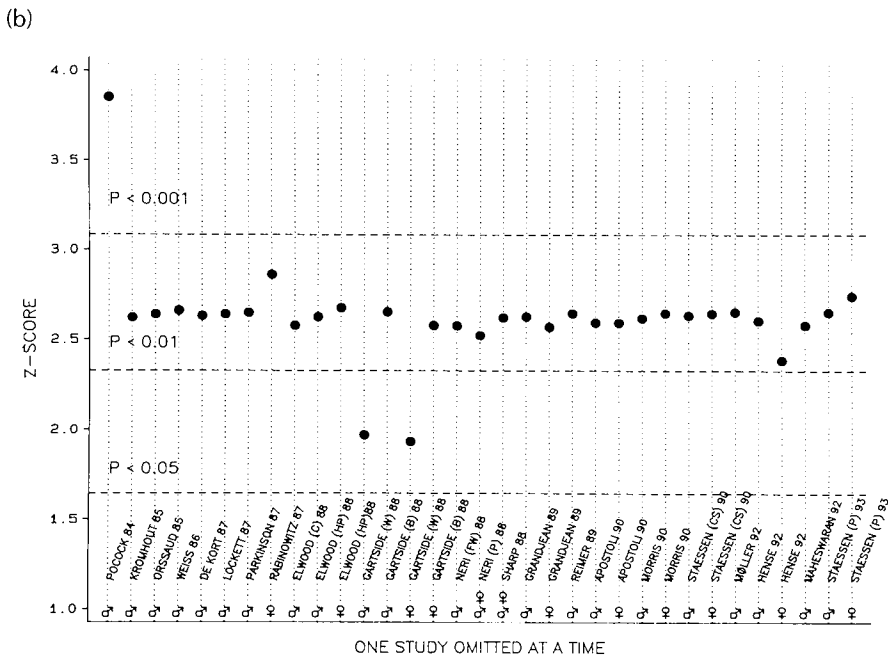


Fig. 3. Sensitivity analysis for systolic (a) and diastolic (b) pressure. For the identification of studies, see Fig. 1.



+2.2 mmHg (+0.7 to +3.6 mmHg; $P=0.006$) for diastolic pressure.

Discussion

The results assessed from the blood lead concentration suggest that there is a weak positive association between blood pressure and lead exposure. Overall, a doubling of blood lead concentrations was associated with a 1.0 mmHg increase in systolic blood pressure and with a 0.6 mmHg rise in diastolic pressure. These overall results must be interpreted with caution. It was assumed

in the analysis that all studies provided an estimate of a common association size. Although the similarity of results across studies did not refute this hypothesis, the various studies took different factors into account as possible confounding factors. This may have affected the estimate of the pooled association size. However, with the exception of age, there is no general agreement on the covariates that should be taken into account in estimating the relationship between blood pressure and blood lead. Some researchers found that alcohol intake and blood haemoglobin concentration were important covariates [54], whereas others discovered significant interactions with race, smoking and caffeine intake, but not with alcohol consumption [51–53].

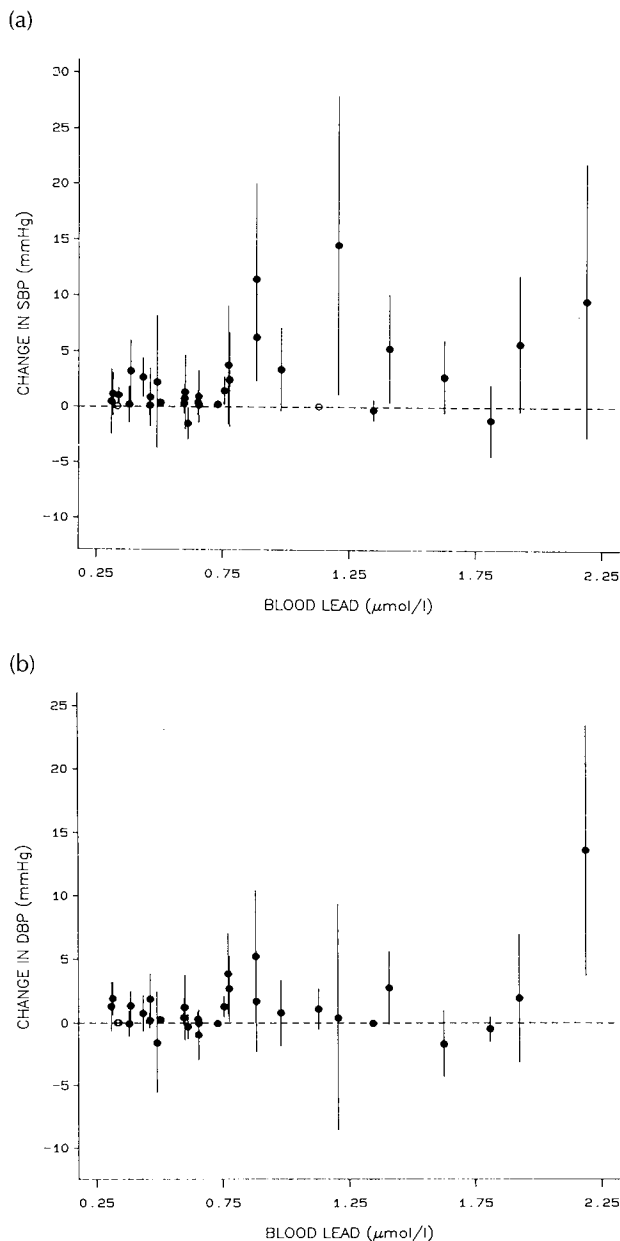


Fig. 4. Change in systolic (a) and diastolic (b) pressure associated with a doubling of blood lead concentration. The association sizes with 95% confidence intervals are plotted as a function of the mean blood lead concentration across 33 groups. \circ , groups for whom a non-significant systolic [50,58] or diastolic [42,58] association size was assumed to be zero.

To calculate the pooled association size, the association between blood pressure and blood lead concentration had to be expressed on a common scale. The change in blood pressure, which would be associated with a doubling of blood lead concentration, was therefore calculated for all groups included in the meta-analysis. A twofold increase in blood lead was chosen as this approximated the range of the non-industrial population means of blood lead (Table 1). Moreover, a doubling of blood lead concentration, which was apparent in all groups, was also observed in real life, as shown by the measures of central tendency and the ranges of the blood lead

concentrations (Table 1). In 19 of the 33 groups included in the meta-analysis, the investigators found that the relationship between blood pressure and blood lead was best described after logarithmic transformation of blood lead concentration levels. For the latter studies, the association size could be calculated simply by multiplying the regression coefficients by 0.30 if common logarithms had been used, or by 0.69 for natural logarithms. For reports in which blood lead was expressed on a linear scale, the blood pressure change associated with a twofold increase of mean blood lead concentration was computed. The point estimates of the association sizes tended to be larger for studies on a linear than on a logarithmic scale, but the 95% CIs showed that the differences between these estimates were not significant.

Blood lead, from which lead exposure was assessed in the present analysis, does not always provide the best available estimate of exposure. If, for instance, exposure ceases but the amount of metabolically active lead in the body remains elevated, blood lead usually falls, whereas zinc protoporphyrin in the blood does not return to control values [68]. Compared with blood lead and with bone lead, which has little biological activity, it has been suggested that zinc protoporphyrin in the blood is a better predictor of the burden on target organs, such as the kidneys and the central nervous system [69]. Measurements of zinc protoporphyrin in blood were available from only a few studies [41,58,62,66,67] but in these reports none of the correlations with blood pressure were statistically significant.

According to the Science Citation Index, studies supporting a hypothesis are cited almost six times more frequently than negative studies [70]. To exclude bias due to the omission of negative but published findings, the present analysis estimated the overall blood pressure effects both with and without the studies [42,50,58] for which the non-significant associations had been assumed to be zero (Table 2). In addition, for nine studies (Table 1), detailed information was made available by the authors. However, these precautions do not address the problem of publication bias. Indeed, research with statistically significant results, confirming a provocative hypothesis or substantiating a favoured line of thinking, is much more likely to be submitted and published than work with non-significant results or with results that were non-significant. A systematic review of literature showed that the likelihood of publication was also greater when the sample size was larger [18]. Moreover, publication bias was more frequent for observational than for laboratory-based research. These observations suggest that overviews of published data should be interpreted with reservation, especially compilations of observational studies [18] such as the present meta-analysis. However, small studies that were not published would make no major impact on the present weighted meta-analysis.

The biological plausibility of a causal relationship between elevated blood pressure and lead exposure has

been mainly investigated in animal experiments and in tests *in vitro* [4]. The most likely mechanisms include impairment of renal function [2], interference with the balance between the renin-angiotensin-aldosterone axis and the renal kallikrein system [9,10,71], direct actions at the level of vascular smooth muscle cells [72], alterations of ion transport across the cellular membranes [35] and potentiation of sympathetic stimulation [73]. However, in the majority of studies, the association between systolic and diastolic blood pressure and blood lead concentration did not reach statistical significance (Fig. 1). There was also no dose-response relationship between mean blood lead concentrations and the association sizes across individual studies (Fig. 4). In the combined studies, the association between blood pressure and blood lead reached statistical significance, but the pooled *P* values were largely influenced by the study of women in the final stages of pregnancy [42] and the NHANES II survey [11,46-49] (Fig. 3). Thus, the present findings do not support the hypothesis that lead exposure plays a major role in the pathogenesis of hypertension. Moreover, epidemiological and observational studies can demonstrate a relationship between an index of exposure and an effect parameter, but they never prove the causality of such a relationship. Any such relationship may be due to a confounding factor and it could be argued that weak and inconsistent associations are more likely to be explained in this way. In an epidemiological study in which a correlation is found, the significance in terms of morbidity and mortality also needs to be evaluated. This last point may be particularly relevant for the lead-blood pressure issue, because hypertension is a major cardiovascular risk factor [74].

In the present analysis, the increase in blood pressure that would be associated with a twofold rise in blood lead concentration was considerably smaller than some earlier estimates [11]. Assuming that there is a causal and reversible relationship between blood pressure and blood lead, the potential health risks of lead exposure have previously been examined in white men by extrapolating data from the multiple logistic regression models obtained in the Framingham Study [74] and in the Pooling Project [75]. These calculations suggested that a 37% decline in blood lead concentration, as observed in the USA from 1976 to 1980 [76], would, over 10 years, result in a 5% fall in the incidence of fatal and non-fatal myocardial infarction, a 7% decrease in the rate of fatal and non-fatal strokes and a 5-6% decrease in total mortality [11]. However, no prospective data are yet available to substantiate these claims. The mortality studies in heavily exposed workers have not demonstrated any excess cardiovascular mortality [4], and theoretical considerations may not agree with subsequent observations. For instance, the use of the contraceptive pill in middle-aged women was known to increase blood pressure by an average of 5 mmHg systolic and 1-2 mmHg diastolic [77,78] and to increase the risk of overt hypertension by three to six times [77]. Subsequent prospective studies,

however, failed to show any marked excess risk of cardiovascular disease attributable to the contraceptive pill [78].

In conclusion, the question of whether low-level lead exposure results in an increase in blood pressure in the general population remains unanswered because the causal nature of the correlation is unproven and because it cannot be reproduced with zinc protoporphyrin in blood as an index of exposure [41,56,62,66,67]. The published literature suggests that there can be only a weak positive association between blood pressure and blood lead concentration. Nevertheless, these assumptions need to be assessed in prospective population studies.

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