Environmental Health Perspectives
Vol. 78, pp. 23–30, 1988

The Relationship Between Blood Lead, Blood Pressure, Stroke, and Heart Attacks in Middle-Aged British Men

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The relationship between blood lead concentration and blood pressure is examined in a survey of 7371 men aged 40 to 59 from 24 British towns. After allowance for relevant confounding variables, including town of residence and alcohol consumption, there exists a very weak but statistically significant positive association between blood lead and both systolic and diastolic blood pressure. These cross-sectional data indicate that an estimated mean increase of 1.45 mm Hg in systolic blood pressure occurs for every doubling of blood lead concentration with a 95% confidence interval of 0.47 to 2.43 mm Hg.

After 6 years of follow-up, 316 of these men had major ischemic heart disease, and 66 had a stroke. After allowance for the confounding effects of cigarette smoking and town of residence there is no evidence that blood lead is a risk factor for these cardiovascular events. However, as the blood lead-blood pressure association is so weak, it is unlikely that any consequent association between lead and cardiovascular disease could be demonstrated from prospective epidemiological studies.

An overview of data from this and other large epidemiological surveys provides reasonably consistent evidence on lead and blood pressure. While NHANES II data on 2254 U.S. men indicate a slightly stronger association between blood lead and systolic blood pressure, data from two Welsh studies on over 2000 men did not show a statistically significant association. However, the overlapping confidence limits for all these studies suggest that there may be a weak positive statistical association whereby systolic blood pressure is increased by about 1 mm Hg for every doubling of blood lead concentration. Nevertheless, such statistical association cannot be taken as establishing a causal effect of low-level lead exposure on blood pressure, particularly since there are important confounders, e.g., alcohol consumption, which are much more strongly related to blood pressure.

Introduction

The hypothesis that moderate elevations in blood lead concentration are associated with increased blood pressure in humans is supported by considerable experimental evidence in laboratory animals (*1,2*). Since direct experimental evidence in humans cannot be obtained, the principal investigational approach in humans has been with observational studies in representative samples of either the general adult population or occupationally exposed groups.

This paper describes cross-sectional results from one large survey, the British Regional Heart Study (BRHS). Since our original publication on this topic claiming a lack of association between blood lead and blood pressure (*3*), studies of data from the United States National Health and Nutrition Examination Survey (NHANES II) have concluded that there is an important association (*4,5*). Hence, it is opportune to re-examine our data, paying careful attention to the role of confounding factors such as town of residence and alcohol consumption.

In addition, the BRHS is a prospective study, and the men are being followed for fatal or nonfatal cardiovascular events since initial screening. Hence, new results are presented concerning whether moderate elevations in blood lead are related to risk of ischemic heart disease (IHD) or stroke.

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It is unrealistic to expect any single epidemiological study to provide definitive answers concerning blood lead-blood pressure relationships. Therefore, this paper also presents an overview of the collective evidence from all the major surveys in this field and demonstrates a greater consistency of evidence than might be achieved from separate perusal of the findings and conclusions from each individual study.

Methods

The BRHS examined 7735 men aged 40 to 59 who were randomly selected from the age-sex registers of representative general practices in 24 British towns. Details of the selection of towns and general practices and the methods of screening and data collection have previously been reported (*6*). Each man's blood pressure was measured twice in succession with the London School of Hygiene sphygmomanometer, with the subject seated and his arm supported on a cushion. Diastolic blood pressure was recorded at disappearance of sounds (phase V). The mean of two readings of blood pressure was adjusted for observer variation within each town to allow for any inconsistencies among the three observers (*7*).

Blood samples for lead analysis were obtained from 7379 men (95%). Blood lead concentrations were analyzed at the University of Southampton with flame microsampling atomic absorption spectroscopy. A strict quality control protocol was maintained, and the performance of the laboratory was continually monitored by participation in national and international quality assessment schemes for analysis of blood lead concentration.

Alcohol consumption was recorded using questions of frequency and quantity. A drink was defined as half a pint of beer, one glass of wine, or a single shot of spirits. For data analysis, eight drinking categories were used: nondrinker, occasional drinker, weekend drinker (1–2, 3–6, or > 6 drinks a day), and daily drinker (1–2, 3–6, or > 6 drinks a day). For illustration, in Figures 1 and 2 these are combined to

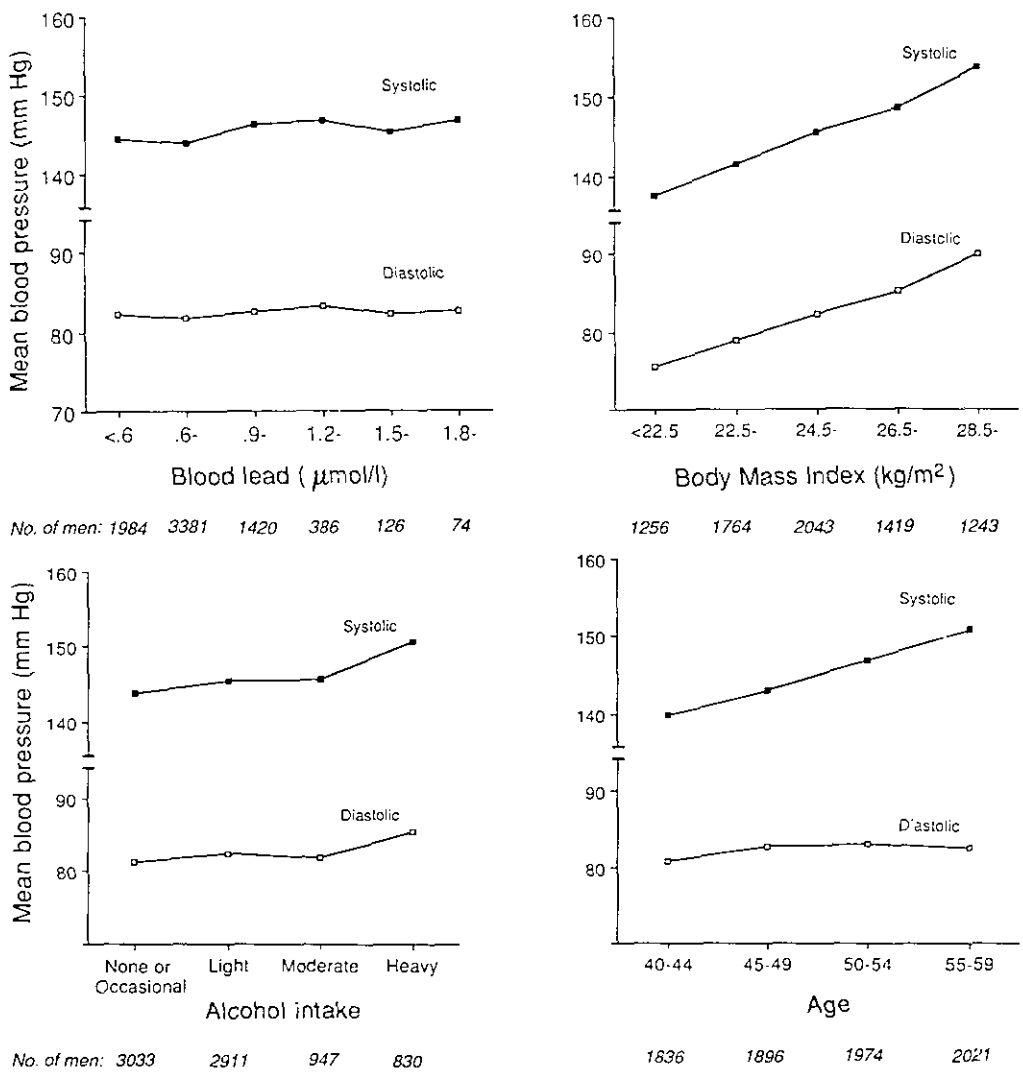

FIGURE 1. Mean systolic and diastolic blood pressures for men categorized by blood lead concentration, body mass index, alcohol consumption, and age.

form four drinking categories: nondrinker or occasional drinker, light drinker (1–2 daily or on weekends), moderate (3–6 daily or on weekends), and heavy drinker (> 6 daily or on weekends).

Cigarette smoking habits derived from a standardized questionnaire were as follows: never smoked cigarettes, ex-cigarette smoker, and current cigarette smoker at four levels (1–19, 20, 21–39, > 40 per day). Ex-cigarette smokers who currently smoked a pipe/cigars are included in ex-cigarette smokers. Those men who had only ever smoked pipe/cigars are included in never smoked cigarettes. For both current and ex-smokers, the number of years a man had smoked cigarettes was also recorded, this variable (smoking years) being a strong smoking-related predictor of IHD risk *(8)*.

All of the 7735 men who were initially examined from 1978 to 1980 were scheduled to be followed up for both morbidity and mortality for 8 years. So far, 99% of the original cohort still alive and living in Great Britain are being followed up. Details of the follow-up procedures have been published *(9)*. All cases of major IHD and stroke occurring between screening and August 1985 are included in this paper.

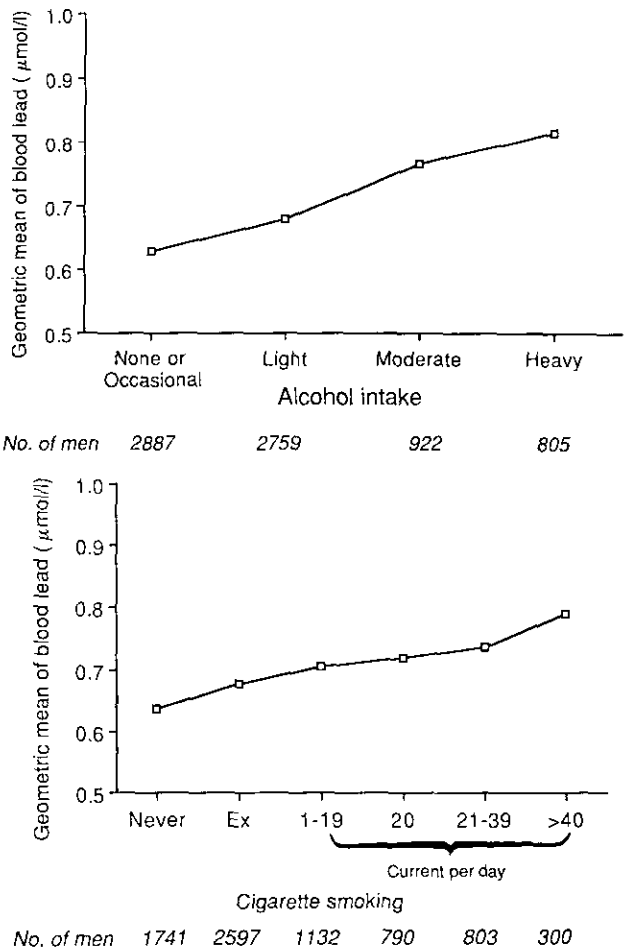

FIGURE 2. Mean blood lead concentration for men categorized by their reported alcohol consumption and cigarette smoking.

Results

Personal Factors Related to Blood Pressure and Blood Lead

Figure 1 shows a simple display of the univariate association between blood lead and blood pressure in the 7371 men for whom both were measured. There is some suggestion of a rise in mean systolic pressure as blood lead increases, but the correlation coefficient is only 0.03. However, there are several personal characteristics in middle-aged men that are known to be associated with blood pressure. For example, Figure 1 also shows the trends in mean systolic and diastolic pressure for these same men grouped according to body mass index, age, and alcohol consumption. Clearly, body mass index and age are important determinants of individual blood pressure, but alcohol consumption is also an important confounding variable in view of its substantial association with blood lead concentration *(10,11)* (Fig. 2), as well as with blood pressure *(6,12)*. Two other relevant personal factors are cigarette smoking and social class. The former is clearly associated with blood lead concentration *(10,11)* (Fig. 2); the latter has weak associations with both blood pressure and blood lead.

Geographic Difference

There are major geographic differences in both mean systolic blood pressure and mean blood lead concentration (Fig. 3). Although there is no evidence of a statistical association for the between-town differences in blood pressure and blood lead, it is still relevant that town of residence should be taken into account when studying this potential lead-blood pressure relationship in individuals.

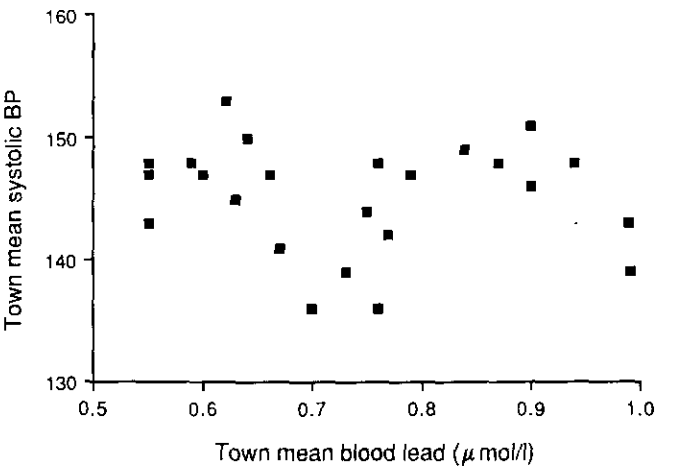

FIGURE 3. The town mean systolic blood pressure plotted against the town mean blood lead concentration for the men resident in each of 24 British towns.

Blood Pressure and Blood Lead (Unadjusted)

Figure 4 provides a more detailed display of mean systolic and diastolic blood pressure according to blood lead concentration. For blood lead between 0.4 and 1.1 μmole/L, mean pressures are shown for each 0.1 μmole/L interval of blood lead. Above 1.1 μmole/L, men are grouped into two categories, 1.2 to 1.3 μmole/L and 1.4 μmole/L or more, so as to preserve approximately 300 men in each category. All the displayed 95% confidence intervals overlap with one another, and also the mean systolic and diastolic blood pressures in the highest blood lead category show no elevation above the average. Thus, detailed univariate analyses show no encouragement for the hypothesis that blood lead and blood pressure are positively associated.

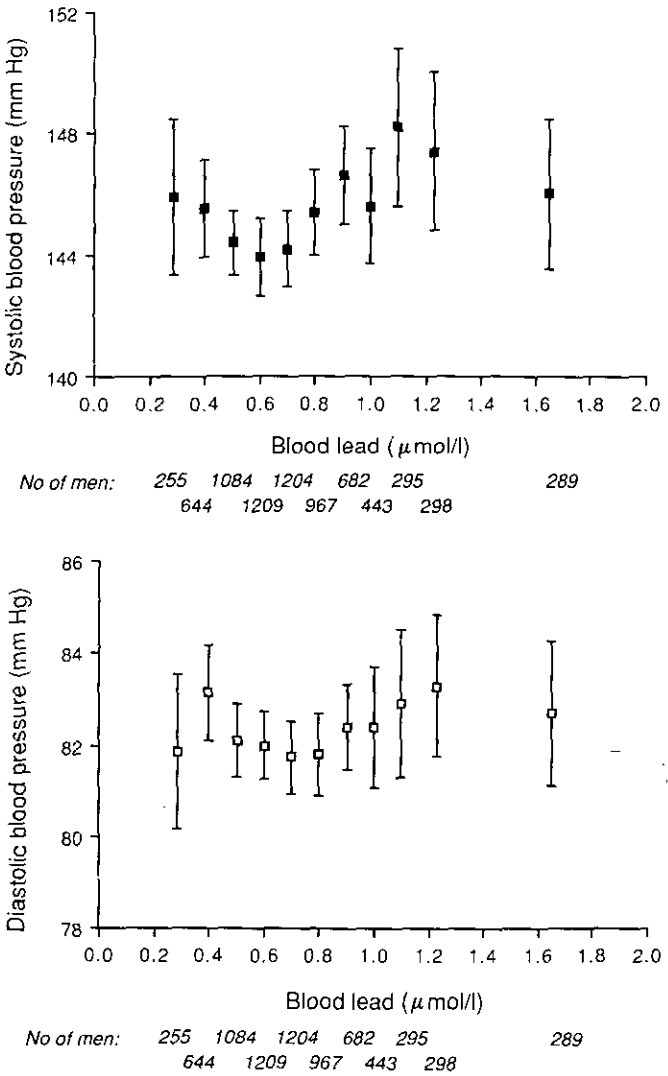

FIGURE 4. Mean systolic and diastolic blood pressures (and their 95% confidence limits) for men categorized in intervals of 0.1 μmole/L of blood lead concentration. (The two highest blood lead groupings are 1.2 to 1.3 μmole/L and 1.4 μmole/L.)

Blood Pressure and Blood Lead (Adjusted for Other Factors)

The situation appears to change once relevant personal factors are taken into account. An analysis of covariance technique has been used to obtain adjusted mean systolic and diastolic blood pressure for each blood lead category, adjustment being for body mass index, age, alcohol consumption (8 categories), cigarette smoking (6 categories), social class (6 categories), and town of residence (24 categories). The consequent plots of adjusted mean systolic and diastolic blood pressure by blood lead in Figure 5 show signs of a weak positive association. Particularly, for the diastolic pressure there is a steady increase in adjusted mean from around 81 mm Hg for blood lead below 0.6 μmole/L to around 83.5 mm Hg for blood lead over 1.0 μmole/L.

Multiple Regression Analysis

This association can be further explored by multiple regressions of systolic and diastolic blood pressure on log(blood lead) and the covariates just mentioned. Table

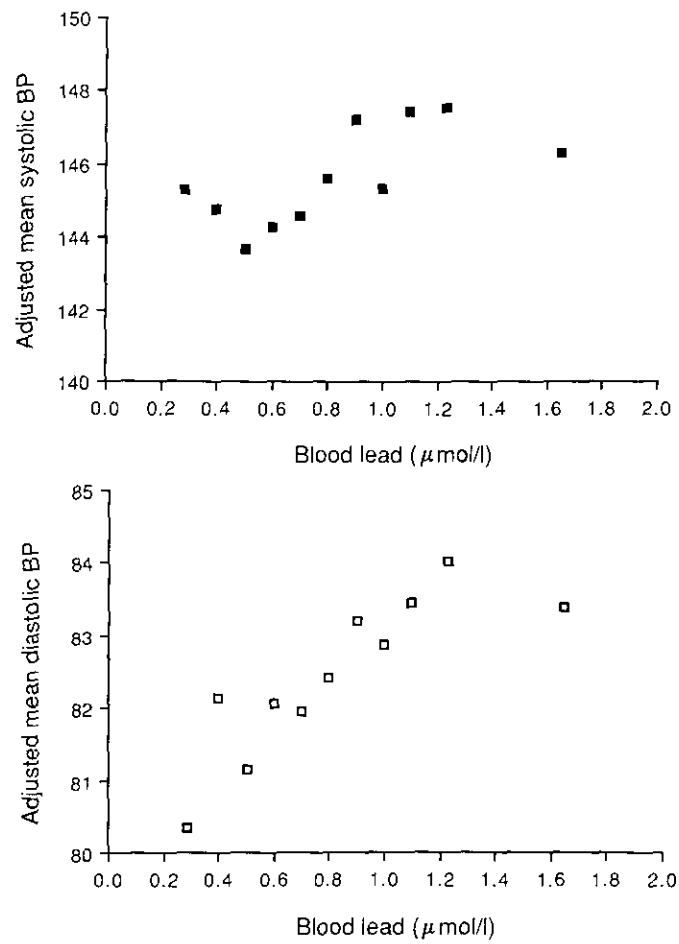

FIGURE 5. Mean systolic and diastolic blood pressures by blood lead concentration after adjustment for body mass index, alcohol consumption, cigarette smoking, social class, and town of residence.

1 shows the regression coefficients for log(blood lead) for three different models: a) unadjusted for other factors; b) adjusted for age, body mass index, alcohol, smoking, and social class; and c) adjusted also for town of residence. The log transform is used because blood lead has a lognormal distribution, the regression fit is slightly improved, and also the findings are then more directly comparable with other studies. In the unadjusted regression, systolic (but not diastolic) blood pressure is significantly associated with log(blood lead). Adjustment for personal characteristics, but not town of residence, renders both the systolic and diastolic regressions on log(blood lead) insignificant. This is chiefly because alcohol consumption is an important confounder, being positively related to both blood pressure and blood lead. Introducing an extra adjustment for town of residence makes both the systolic and diastolic regressions highly statistically significant (p = 0.003 and 0.001, respectively). However, it should be noted that these adjusted statistical associations are still very weak, partial correlation coefficients being 0.04 and 0.05 for the systolic-blood lead and diastolic-blood lead associations, respectively, so that statistical significance is achieved only because of the large number of subjects in the survey.

As a means of quantifying the magnitude of these adjusted relationships, one can use the regression coefficient and its standard error for log(blood lead) to obtain the estimated increase in blood pressure for each doubling of blood lead concentration. This is 1.45 mm Hg for systolic pressure (95% confidence interval, 0.47–2.43 mm Hg) and 1.25 mm Hg for diastolic pressure (95% confidence interval, 0.65–1.85 mm Hg).

Separate Analyses Within Each Town

It is important to remember the geographic basis of the BRHS whereby the sample of 7371 men analyzed here come from 24 towns, approximately 300 men per town. Table 2 shows the results of separate univariate regression analyses of blood pressure on log(blood lead) for the men in each town. These findings demonstrate that the weakness of the blood lead-blood pressure association is such that studies based on a few hundred men contain too much random variation and cannot be expected to produce consistent, precise findings. For instance, the within-town regressions of systolic blood pressure on log(blood lead) produced large significant coefficients in Newcastle and Burnley, while at the other extreme, there were three towns, Hartlepool, Bedford, and Gloucester, with small negative coefficients. In fact, from inspection of the standard errors of each such coefficient, one can see that such differences are largely attributable to random variation, and they are all in broad agreement with a true average regression coefficient of 3.0. Adjustment for alcohol consumption as a confounder reduces this coefficient to 2.0, which is the overall pooled estimate already derived in the multiple regression in Table 1.

Table 1. Regressions of systolic and diastolic blood pressure on ln(blood lead) with and without adjustments for other personal factors and town of residence.

	Regression coefficient for ln(blood lead)	p-value
Systolic blood pressure		
Unadjusted	1.684	0.009
Adjusted for body mass index, age, alcohol, smoking, and social class	0.675	0.28
Adjusted also for town	2.089	0.003
Diastolic blood pressure		
Unadjusted	0.302	0.46
Adjusted for body mass index, age, alcohol, smoking, and social class	−0.063	0.87
Adjusted also for town	1.809	0.001

Table 2. Separate univariate regression analyses for the men in each town.

Town	Regression coefficient (SE): Systolic blood pressure on ln(Pb)		Diastolic blood pressure on ln(Pb)	
Newcastle	11.4	(4.3)	4.4	(2.9)
Burnley	10.6	(3.4)	7.2	(2.2)
Dewsbury	5.8	(3.5)	2.7	(2.4)
Wigan	5.6	(3.1)	2.6	(1.8)
Southport	5.6	(4.3)	3.8	(2.3)
Harrogate	5.5	(4.1)	4.8	(2.5)
Merthyr Tydfil	5.5	(4.2)	3.2	(2.3)
Darlington	5.0	(3.5)	−3.0	(2.2)
Mansfield	5.0	(4.4)	6.1	(2.6)
Falkirk	4.2	(4.0)	−0.4	(2.8)
Shrewsbury	3.8	(4.3)	1.9	(2.6)
Grimsby	2.8	(2.9)	1.6	(1.7)
Guildford	2.5	(3.8)	2.5	(2.3)
Ipswich	2.0	(2.9)	−0.5	(1.9)
Scunthorpe	1.9	(2.8)	3.0	(1.7)
Ayr	1.6	(2.8)	0.7	(1.8)
Exeter	1.5	(3.0)	−0.4	(2.2)
Carlisle	1.3	(3.0)	1.8	(1.8)
Lowestoft	1.0	(3.9)	−2.2	(2.4)
Maidstone	0.9	(2.9)	1.2	(1.9)
Dunfermline	0.6	(3.5)	−0.2	(2.2)
Hartlepool	−1.4	(3.4)	0.8	(2.0)
Bedford	−1.7	(4.5)	5.1	(2.8)
Gloucester	−3.1	(4.4)	2.4	(2.8)

Blood Lead and Cardiovascular Events

Table 3 shows the mean blood lead concentration for 316 men who have experienced major ischemic heart disease since initial screening compared with the 7063 other men. The mean blood level concentration is significantly higher in these IHD cases (p = 0.01), but this is without taking account of important confounding variables. In particular, cigarette smoking is an established risk factor for IHD, which also elevates blood lead concentrations (Fig. 2). The towns with higher IHD mortality tend to have slightly higher blood lead concentrations, perhaps because blood lead levels are higher in soft water areas (*13*), which are known to have higher IHD mortality (*14,15*). Therefore, analysis of covariance has been used to obtain an

Table 3. Mean blood lead concentrations for men with subsequent ischemic heart disease and stroke compared with other men, with and without adjustment for age, smoking years, and town of residence.

	IHD cases	Other men	Stroke cases	Other men
No. of men	316	7063	66	7313
Mean blood lead, μmole/L	0.786	0.735	0.808	0.737
Difference in means ± SE	0.051	±0.019	0.071	±0.049
Difference in means ± SE after adjustment for age, smoking years, and town	0.014	±0.015	0.033	±0.033

adjusted difference in mean blood lead between IHD cases and other men adjustment being for age, number of years smoking cigarettes, and town of residence (24 categories). This adjustment has reduced the mean excess in blood lead among IHD cases from 0.051 μmole/L to 0.014 μmole/L, which is no longer significantly different from zero. Table 3 also shows similar results for the 66 cases of stroke compared with other men.

An alternative method of studying blood lead as a possible IHD risk factor is to estimate the relative odds of becoming an IHD case for different intervals of blood lead. Using the 1986 men with blood lead concentration under 0.6 μmole/L as a reference group, Figure 6 shows that the odds (or risk) of IHD is somewhat greater at higher blood lead concentrations, particularly at 1.2 μmole/L or more. However, use of logistic regression analysis to obtain relative odds adjusted for age, smoking years, and town of residence shows no evidence of an excess risk of IHD at these higher blood lead concentrations.

Overview of Other Large Studies of Blood Lead-Blood Pressure Relationships

In any specific field of epidemiological research, no single observational study can be relied upon to provide a definitive answer, particularly when the relationship under study is quite weak and in the presence of strong potential confounders. In this preliminary attempt to present the collective evidence from ours and other studies of the lead-blood pressure relationship, attention is confined to the larger studies for which appropriate regressions of systolic blood pressure on blood lead are available. As already illustrated in Table 2, studies on a few hundred subjects can produce highly variable estimates of the lead-blood pressure association. Also, the available data in such smaller studies are liable to suffer from publication bias, whereby the more positive small studies are more likely to be published. Studies of under 500 subjects will therefore not be mentioned further. All results presented refer to males only.

For each study we present the estimated change in mean systolic blood pressure for a doubling of blood lead. This is obtained from the principal regression analysis that the authors selected. These findings are displayed in Figure 7 with the 95% confidence limits. For the BRHS these results are directly obtained from the regression coefficient for log(blood lead) after adjustment for town of residence and other covariates (Table 1). For NHANES II, the results are similarly determined from data on 2254 males aged 20 to 74 after adjustment for site and several other biochemical, dietary, and personal factors (*16*). For the two Welsh studies on 1164 and 865 men, respectively, linear regression was used, adjusting for age only, and hence we have plotted the mean change in systolic blood pressure for one specific doubling of blood lead concentration (8 to 16 μg/dL) in the middle of their blood lead distributions.

The two Welsh studies show no significant association, whereas NHANES II data show an estimated increase of 2.24 mm Hg in systolic blood pressure for a doubling of blood lead concentration, which is larger than in the BRHS. However, the overlapping confidence intervals indicate that these findings are not consistent, and all studies are compatible with a possible increase in systolic blood pressure of approxi-

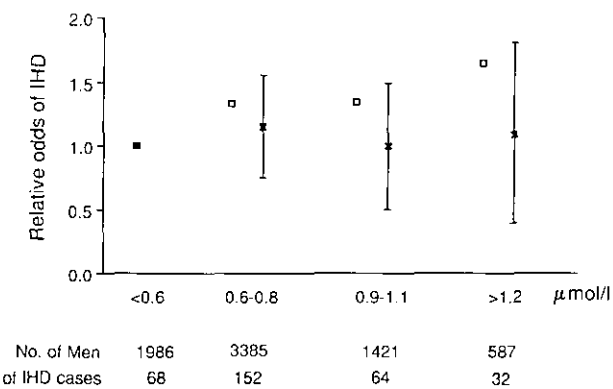

FIGURE 6. Relative odds of major IHD for men categorized by blood lead concentration: (■) base group (< 0.6 μmole/L); (□) unadjusted for other factors; (x) adjusted for age, smoking years, and town of residence, together with 95 % confidence limits.

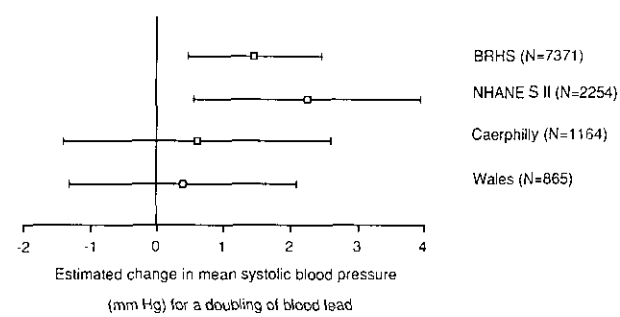

FIGURE 7. An overview of four large studies relating systolic blood pressure to blood lead concentration. The graph shows each study's estimated change in mean systolic blood pressure for each doubling of blood lead (e.g., from 8–16 μg/dL) together with 95% confidence limits. (Two other large studies in Canada and Denmark showed no significant association, but estimates are not known to us.)

mately 1 to 2 mm Hg for a doubling of blood lead concentration. It should also be noted that two other studies in Canada (*18*) and Denmark (*19*) on 2193 and 950 subjects, respectively, have found no significant association, but we do not have their regression results available as yet. This would imply that the lower figure of 1 mm Hg systolic increase per doubling of blood lead is more plausible.

Discussion

Blood Lead and Blood Pressure in BRHS and NHANES II

Earlier publications on lead and blood pressure from the BRHS (*3*) and NHANES II (*5*) have appeared to reach widely divergent conclusions; this journal issue provides an opportunity for reassessment of these two studies using comparable statistical approaches. While NHANES II continues to show a markedly stronger relationship in the selected subgroup of white males aged 40 to 59, this discrepancy is largely removed once one compares regression results for all adult males in the two studies.

Alcohol Consumption

The choice of other covariates as potential confounders has had an important effect on the two studies' results. In the BRHS, alcohol consumption is of particular importance, being positively related to blood pressure and blood lead. It should be noted that the alcohol-blood pressure relation in the BRHS is virtually unaffected by adjustment for blood lead levels, indicating that alcohol's effect on blood pressure is not produced by any lead-related mechanism, such as the lead content of alcoholic drinks. This supports the view that alcohol is a genuine confounder. It is impossible to obtain a fully comprehensive measure of alcohol consumption by simple questionnaire (e.g., in the BRHS, all men drinking over six units per day are grouped together, and this may mean that the alcohol-related component in the univariate lead-blood pressure relationship is not completely allowed for in the multiple regression. This same point relates to NHANES II, as their information on alcohol was not very detailed.

Allowance for Geographic Differences

Both NHANES II and the BRHS are cross-sectional surveys among individuals from many geographical areas. They have a two-stage design, the first being nonrandom selection of geographic locations and the second being random selection of individuals from a defined sampling frame in each location. It has now become recognized that particularly when studying a weak statistical association such as lead and blood pressure it is important to take account of this geographical component to the study. In the BRHS, failure to adjust for town of residence actually underplayed the significance of the statistical association. However, in NHANES II, the strength of association was reduced after adjustment for site, perhaps because sites with higher mean blood pressure tended to have higher mean blood lead levels, possibly as a consequence of the time trends in both blood lead and percent urban dwellers at the sampling sites.

Overview of Major Studies

In our overview of the major studies in this field (Fig. 7) we have aimed for an objective quantification of the magnitudes of association between blood lead and systolic blood pressure. Subjective assessment of such data tend to classify studies as either significant or nonsignificant, but this dichotomous attitude toward assessment of scientific hypotheses is oversimplistic and counter-productive. It fails to take account of the limited power that individual studies have to detect weak relationships. We have been able to demonstrate some consistency between the larger studies suggestive of a very weak positive association, but it is also important to realize the limitations of this approach. Specifically, the different studies have adopted very different strategies toward the selection of other covariates to be used in the regression models. For instance, the BRHS selected a limited set of personal covariates related to blood pressure and blood lead, whereas NHANES II did an extensive selection process across a wide range of personal, biochemical, and dietary data. The Welsh analyses undertaken thus far have only adjusted for age. Greater consistency in the handling of confounders would provide more reassurance as to the validity of our overview approach. However, a previous NHANES II report (*5*) has claimed a stability of blood lead-blood pressure association for several different approaches to selecting covariates in their data. Therefore, it seems plausible to argue that the overall assessment of the data on all available studies is not likely to be changed substantially by further statistical analysis.

Interpretation of the Statistical Association

The crucial issue is whether this evidence of a weak statistical association is evidence of a causal effect of low-level lead exposure. Here we need to accept the limitations of observational epidemiology, which cannot provide definitive evidence of a causal link. Furthermore, the strength of statistical evidence here is not substantial. The difficulty of completely allowing for important confounders, e.g., alcohol consumption and the fact that only two of the six largest studies have achieved statistical significance, would suggest that this is one area where the epidemiological approach cannot provide a clear answer. It would be premature to conclude that these statistical findings are of practical relevance to public health.

Blood Lead, Heart Attacks, and Strokes

We are not aware of any previous prospective epidemiological studies of coronary heart disease and stroke that have included blood lead as a potential risk factor. However, it has been hypothesized that trace metals such as lead may explain the relationship between soft water and cardiovascular disease and also that clinical lead poisoning includes signs suggestive of a toxic effect on the heart (*20*). Also, Pirkle et al. (*5*) have extrapolated from their blood lead-blood pressure relationship in NHANES II data to argue that there could be substantial reductions in the numbers of strokes and heart attacks as a result of the decline in blood lead levels in the United States since the mid-1970s.

In this paper we have shown that mean blood lead levels are somewhat higher in individuals who subsequently have a heart attack or stroke. However, after allowance for cigarette smoking and town of residence, this association is no longer statistically significant. One cannot automatically infer that low-level lead exposure has no effect on risk of stroke and heart attack, but the evidence clearly indicates that lead is not a major contributor to risk of cardiovascular disease. It is still worth considering whether a possible blood lead-blood pressure relationship could have implications for risk of major cardiovascular events, but the estimates provided by earlier research (*5*) would seem extravagant, as the collective evidence suggests a much weaker blood lead-blood pressure relationship than they have previously claimed. Thus, there remains the possibility that an extremely small proportion (less than 1%) of strokes and heart attacks could be prevented by substantial reductions in mean blood lead concentration in the general population. This inference depends on a causal interpretation of statistical associations, but we have no direct evidence that changes in population lead levels would actually affect the population's blood pressure, and there even remains controversy over whether lowering of blood pressure reduces the risk of heart attacks (*21*). In conclusion, we see no convincing epidemiological evidence at present to support the claim that moderate elevations in body lead burden are of relevance to the risk of cardiovascular disease.

The British Regional Heart Study is a British Heart Foundation Research Group and is also supported by the Medical Research Council, Department of Health and Social Security, the Scottish Endowment Research Trust and the Chest Heart and Stroke Association. Estimation of blood lead concentrations was supported by the Department of Health and Social Security.

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