

Blood Lead and Blood Pressure: Analysis of Cross-Sectional and Longitudinal Data from Canada

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Analysis of data collected during the Canada Health Survey of 1978-1979 indicated a positive relationship between blood lead and blood pressure, but so weak that the range of lead-related variation among members of the general public was estimated to be at most 3.0 mm Hg of diastolic pressure. Even so, a blood lead level in excess of the median value of 10 µg/dL entailed a 37% higher risk of having diastolic pressure above 90 mm Hg.

In a longitudinal study of lead foundry workers, an association was found between short-term changes in an individual's blood lead level and contemporary changes in diastolic pressure; this remained significant after allowance for age (or time) trends and for effects attributable to changes in body weight. Short-term changes in urinary cadmium levels were similarly predictive of diastolic pressure.

In the controversy that followed the publication of the results of Harlan et al. analysis of the NHANES data (1), indicating the possibility of a causal relationship between blood lead levels and blood pressure, there were those who argued that the relationship found merely reflected the concurrent time trends of these two causally unrelated variables. It seemed to us that the most nearly appropriate source of independently acquired data from which to confirm the type of relationship described by Harlan et al. should this be a feature of the North American population as a whole, was the Canada Health Survey (CHS) (2).

Cross-Sectional Study of General Population Sample

A particular merit of the Canadian population data is that the data were collected during the period of only 10 months, during 1978-1979, compared with 49 months which elapsed during NHANES II. This

greatly reduces the risk of confounding between blood lead and any unidentified variable that happened to have a similar time trend. Details of design, as well as descriptive statistics derived from the CHS, have been published by the responsible government agencies. Analysis has been focused on persons aged 25 and over, and we have generally excluded that part of the population over the age of 65 which has already been substantially depleted by cardiovascular deaths so that hypertensive status among the survivors is harder to interpret. Subjects under treatment for hypertension were excluded from our analyses, except in those cases where they appear as a separate class. As separate regressions for males and females gave substantially similar results, it was decided to use both sexes together.

For 2193 CHS subjects aged 25 to 64, the zero-order correlation between diastolic blood pressure and blood lead level was found to be 0.115. Though this association is a weak one (as was also the case in the NHANES II data), its statistical significance is not in doubt ($p < 0.001$). It must be noted that the strength of the association owes something to the circumstance that males tend to have higher values than females both for blood pressure and for blood lead. Because of the well-known tendency of blood pressure to increase with age, it was appropriate to use age as a control variable, even though there is no strong or regular relationship

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between age and blood lead in the CHS. The next most important control variable was body build [indexed in the CHS by the ratio weight (kg)/height² (m)], which had a fairly strong correlation with blood lead in the CHS ($r = 0.257$).

After examining all the intercorrelations among nine possible confounder variables, two were selected for inclusion, namely serum zinc and hemoglobin level, so that the multiple regression equations computed had up to six independent variables. In addition to the linear model, we also used models in which blood lead measurements were subjected to logarithmic transformations. In contrast to the NHANES II data where the minimum blood lead concentration of 9933 values was 2 $\mu\text{g/dL}$ (1), the CHS data included a substantial number of values below the limit of detection, making it necessary to add some positive quantity to the recorded value of zero before taking the logarithm: We experimented with arbitrary constants set at 0.1, 1.0, 3.0, and 5.0, and also with a function of the recorded value set so as to make cumulative frequency distribution of the logged values exactly Gaussian.

Table 1 shows results of testing the one-sided alternative hypothesis that there is a positive relationship between blood lead level and blood pressure (excluding subjects on antihypertensive medication). Table 1 shows p -values that were derived from F -ratios associated with the regression coefficient on blood lead in each model. All but one version of the regression employing three control variables attained significance at the conventional 5% level, but none of those employing control for zinc and hemoglobin attained significance.

From the right-hand column of Table 1, it appears that the amount of influence ascribed to blood lead by the logarithmic model may be very sensitive to the adjustment used. The estimated change in blood pressure per unit change in the transformed lead measurement ranged from as low as 0.10 [with $\ln(x + 0.1)$] to 0.68 [with $\ln(x + f(x))$].

Using the parameter estimate given in Pirkle et al. (3) with the logarithmic model, the reduction in mean pressure achieved by successive 5.0 $\mu\text{g/dL}$ reductions, starting from 20.0 $\mu\text{g/dL}$, would be as

Table 1. Significance of partial regression coefficients of diastolic blood pressure on blood lead level.^a

Model	p -Values	
	Three control variables ^b	Five control variables ^c
Linear	0.041	0.104
Logarithmic		
$\ln(x + 0.01)$	0.113	0.242
$\ln(x + 1.0)$	0.034	0.114
$\ln(x + 3.0)$	0.032	0.108
$\ln(x + 5.0)$	0.033	0.107
$\ln(x + f(x))$ ^d	0.039	0.114

^aSubjects not on antihypertensive medication.

^bVariables: age, sex, body build.

^cVariables: age, sex, body build, percent hemoglobin, serum zinc.

^d $f(x)$ chosen to make lead variable exactly log-normal.

Table 2. Predicted difference in mean diastolic blood pressure between subjects whose blood lead levels are 0.0 $\mu\text{g/dL}$ and 47 $\mu\text{g/dL}$.^a

Model	Difference in mean diastolic blood pressure, mm Hg	
	Three control variables ^b	Five control variables ^b
Linear	3.0	2.1
$\ln(x + 0.01)$	2.1	1.4

^aData of Canada Health Survey for subjects not on antihypertensive medication.

follows: 1.14 mm Hg, 1.60 mm Hg, 2.74 mm Hg, and something in excess of 6.4 mm Hg. If this model (with the same parameter estimate) described the Canadian population, then we should expect to find a more than 15-mm Hg difference in mean diastolic blood pressure between the extremes of blood lead level seen in CHS subjects (namely, 47 $\mu\text{g/dL}$ and 0, taken here as 1.0 $\mu\text{g/dL}$). In fact, as Table 2 shows, the range of lead-related variation in blood pressure apparent in Canadian data is estimated to be at most 3.0 mm Hg (that is 0.064 mm Hg per unit of blood lead) and possibly not over 1.4 mm Hg.

An attempt has been made to obtain another perspective on the possible public health significance of the lead/blood pressure association by using an analysis based on categories (such as blood pressure above/below 90 mm Hg), as distinct from the regression analysis based on blood pressure as a continuous variable. For this purpose we calculated prevalence rates of antihypertensive medication use and of elevated blood pressure, using as numerators and denominators estimates for the Canadian population furnished by Health and Welfare Canada. Thus, this analysis adjusted for the design effects of the CHS, which our unweighted regression analysis did not. [In the regression analysis of CHS blood pressure data in relation to alcohol consumption carried out by Coates et al. (4), it was found that adjustment for design effects made little difference to the results obtained.] On the other hand, the prevalence analysis used included only two control variables: sex and body build (with 25 as the boundary value of the index separating "slim" from "not-so-slim").

Table 3 shows prevalence rates for the characteristic "using antihypertensive medication" and (within the population not using such medication) for the characteristic "diastolic blood pressure over 90 mm Hg." Table 4 gives estimates of relative risk (RR) derived from an (unweighted) log-linear analysis of the prevalence rates shown in Table 3. As expected, males are substantially more likely than females to have elevated blood pressure ($RR = 1.64$), but less likely to have sought (or to have complied with) medical treatment for it ($RR = 0.62$). Body builds other than slim entail a fourfold risk of antihypertensive medication and, in untreated subjects, a doubling of the prevalence of elevated blood pressure (over 90 mm Hg). The influence of blood lead appears to be much weaker than

Table 3. Prevalence of two mutually exclusive conditions suggestive of hypertension.^a

Condition	Blood lead level, $\mu\text{g}/\text{dL}$			
	Males		Females	
	< 10	≥ 10	< 10	≥ 10
Slim^b				
Use medication, %	0.91	8.84	3.98	2.74
Diastolic pressure > 90 mm Hg, %	12.0	18.0	6.4	7.3
Not so slim^c				
Use medication, %	10.95	5.75	17.56	17.45
Diastolic pressure > 90 mm Hg, %	24.7	25.7	17.9	22.9

^aCanadians age 25 to 64 years.^bWeight/height² < 25.^cWeight/height² > 25.**Table 4. Relative risk of two conditions suggestive of hypertension associated with three independently acting risk factors.**

Risk factor	On antihypertension medication	Diastolic blood pressure > 90 mm Hg and not on antihypertension medication
Sex, male	0.62 (0.23–1.63) ^a	1.64 (1.09–2.44)
Body build, weight/height ² > 25.0	3.85 (0.89–16.6)	2.25 (1.50–3.40)
Blood lead, > 10 $\mu\text{g}/\text{dL}$	1.37 (0.06–31.4)	1.23 (1.02–1.48)

^aNumbers in parentheses are confidence limits.

that of either of these control variables and, in the case of drug use, only one of the four widely varying estimates of relative risk obtained from Table 3 exceeds unity. In the case of elevated blood pressure, however, all four of the independent estimates of relative risk exceed unity and, provided this is agreed to be a one-tailed test situation, we may conclude that the average of these values provides conventionally significant evidence against the null hypothesis ($t = 2.61$, using the logarithms of the four estimates).

Our overall conclusion up to this point was that Canadian data were at least weakly supportive of the inference drawn from NHANES II, in that elevation of blood lead did seem to entail some risk of blood pressure elevation. It would have been premature, in the absence of longitudinal data, to infer that this was a cause-and-effect relationship.

Longitudinal Study of an Occupationally Exposed Group

A search was therefore made in Canada for any group of subjects whose blood lead levels and blood pressure had been measured repeatedly. By studying the variation within individual subjects over time, it was hoped to obtain control over most of the potential confounders that could afflict a cross-sectional study, while the inclusion of age as an independent variable

would control for time trends. A suitable study population was identified at foundry B, where over 500 subjects had been examined annually for periods of up to 14 years.

Though the blood pressure records showed some evidence of digit preference (excessive numbers of even values and multiples of 5), the overall distribution was in good agreement with expectation, having an individual variance (diastolic) of about 100 mm² Hg. This body of data was therefore judged suitable for testing the hypothesis that, within individuals, blood pressure and blood lead level tend to rise and fall together. Statistically significant support for the latter hypothesis would enhance the credibility of a cause-and-effect relationship between the two variables.

Preliminary analysis was carried out by multiple linear regression using the individual employee as the unit of study, with blood pressure (either diastolic or systolic) as the dependent variable. Although for the majority of subjects data are available for 14 years, the present report shows results based exclusively on the period 1979–1985.

From a total of 288 regression estimates of the dependence of diastolic pressure on age, we see in Table 5 that the average rate of increase was 1.161 mm Hg per year. Likewise, each additional kilogram of body weight added an average of 0.312 mm Hg to the diastolic pressure. (Because the height of each adult subject could be assumed constant, weight, rather than its ratio to height, was used in the longitudinal analysis.) From these same equations the average change in diastolic pressure per microgram per deciliter of lead was estimated to be 0.298 mm Hg, a quantity that exceeds 2.5 times its standard error. The corresponding value for systolic blood pressure was only 0.210 mm Hg, which falls just short of conventional significance (one-tailed $p = 0.064$).

Interpretation of these results should take into account the concurrent exposure of lead workers to cadmium in the smelter environment, since cadmium has been implicated both in experimental and clinical studies of hypertension. Fortunately, determinations of urinary cadmium were begun on a routine basis in 1979 and were available for all subjects included in the analysis described previously. As more data accumu-

Table 5. Estimates of mean change in blood pressure per unit change in certain other variables.

Variable	Mean change, mm Hg	
	Diastolic	Systolic
Age, per year	1.161 \pm 0.293 $t = 3.96$	0.502 \pm 0.355 $t = 1.41$
Weight, per kg	0.312 \pm 0.172 $t = 1.81$	0.356 \pm 0.185 $t = 1.93$
Blood lead, per $\mu\text{g}/\text{dL}$	0.298 \pm 0.111 $t = 2.67$	0.210 \pm 0.139 $t = 1.52$
Critical values of t_{285}	2-tailed	1-tailed
5% level	1.97	1.65
1% level	2.59	2.34

late, the possibility of distinguishing between the effects of these two metals will improve. Table 6 shows results of a regression analysis in which cadmium, as well as lead, has been used as an independent variable. However, because of the limited number of data points per subject, it was necessary at this stage to exclude the weight variable, so the results are not directly comparable with those in Table 5. The mean values of the coefficients for lead and cadmium are both positive, but neither can be considered independently significant. Of the two coefficients, that related to cadmium is likely to be the more attenuated by instability of urinary cadmium levels. We also calculated 281 within-subject regression equations for diastolic pressure using cadmium instead of blood lead, while retaining age and body weight as control variables. In 214 of these equations (a proportion of 0.562), the coefficient for cadmium was positive, a clearly significant result ($p = 0.008$). In the corresponding analysis for systolic pressure, the proportion of positive coefficients was only 0.441, again failing to match the effect seen for diastolic pressure.

Within this occupationally exposed group, there is known to be a positive correlation between the levels of these two metals: This may well be the case also in the population at large. The problem of distinguishing a lead effect from a cadmium effect must therefore be of concern for all investigators in this field.

Two other points also have to be considered: *a*) the form of the dose-response relationship (bearing both on the reconciliation of results from occupationally exposed groups with those from general population samples, and on the public health use one can make of the estimates), and *b*) the question of time lag or cum-

ulative effects. These points are discussed in the following section.

Discussion

An assumption of the present analysis was that any dependence of blood pressure on lead level would be simply linear. In the analysis of Pirkle et al. (3), a logarithmic model was postulated, under which a given absolute increment in blood lead level would have a much greater effect on a subject in the lower (general population) range than on one in the upper (occupationally exposed) range. Examination of a subset of foundry B employees whose lead levels showed especially large fluctuations on a ratio scale (at least doubling or halving within the period of observation) produced no support for the idea of a dependence of blood pressure on logarithm of lead level.

A second, and less comfortable assumption was that the effects on blood pressure of variation in blood lead level (and also of variation in body weight) would be expressed immediately, or after an interval that was short in relation to the interval between examinations (usually about 12 months). If this assumption is incorrect, then the association between blood pressure and blood lead (as well as body weight) could be more regular and more important than present results suggest.

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Table 6. Estimates of mean change in blood pressure per unit change in certain other variables.

Variable	Mean change in diastolic pressure, mm Hg	
Age, per year	1.483 \pm 0.185 $t = 8.03$	
Blood lead, per $\mu\text{g}/\text{dL}$	0.079 \pm 0.096 $t = 0.82$	
Urinary cadmium, per $\mu\text{g}/\text{dL}$	0.262 \pm 0.518 $t = 0.51$	
Critical values of t_{282}	2-tailed	1-tailed
5% level	1.97	1.65
1% level	2.59	2.34