

October 24, 1984

Subject: Comments on study by JM Pirkle et al. on blood lead and blood pressure, as presented orally on October 23, 1984

From: Dr. Robert Chapman, HERL RSC

To: Dr. David Weil, ECAO

The authors statistically analyzed data from the Second National Health and Nutrition Examination Survey (NHANES) to characterize the degree of association between blood lead level (BL) and systolic and diastolic blood pressure (BP). They analyzed data from white males aged 40 through 59 years. In a virtually exhaustive series of regression models, employing independent variables singly and in combination, they tested BP against BL and a variety of nutritional, biochemical, demographic, and socioeconomic variables. They consistently observed a positive independent association, statistically significant at $\alpha=0.05$, of BL with systolic and diastolic BP. The magnitude of this association varied by only about 10% across the many statistical models employed.

NHANES population samples are carefully drawn. Laboratory analysis of blood lead levels was subject to very good quality control. The observed relationship between BL and BP is consistent with the limited amount of available information on this subject. A plausible biologic mechanism for the relationship can be postulated. The magnitude of the observed association also impresses me as reasonable; it is not vanishingly small, yet it does not seem unrealistically large.

Though this work is presented as a cross-sectional study, data were actually collected over a four-year span. Also, data were collected in widely separated areas throughout the U.S. These conditions tend to increase the chance of a secondary association of BL and BP with unmeasured temporal or geographic factors. The authors have already constructed statistical models to adjust for both types of factors, and I think it unlikely that they would materially have affected the observed results. However, the effectiveness of their statistical treatment is difficult to evaluate before the paper is published.

Other covariates with possible relationships to BP, such as pulse rate and uric acid, were not treated in this study. However, these variables do not appear to be strongly correlated with BP, and the authors did treat variables known to influence BP. Thus it seems most unlikely to me that inclusion of these covariates would have affected the study's results.

The authors statistically challenged the observed BP-BL relationship in every way that their data set would allow. At the same time, the large number of statistical models employed may lend a somewhat misleading weight to the observed results. Many of the models appear to have covered essentially the same statistical ground as previous models. Also, some models were constructed not specifically to challenge the association of BP with BL, but rather to determine the functional form of the BL variable which explained maximal variation in BP. I think that fewer statistical manipulations could have produced results at least as convincing as those presented.

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The authors estimated absolute decrements and percent reductions in heart attacks, strokes, and deaths expected to accompany reductions in BL. The absolute decrements are subject to considerable uncertainty. The percent reductions are probably more stable, since they are based on multiple logistic models, which yield proportional estimates, not absolute ones.

On balance I agree with the authors that this study shows a probable causal relation between BL and BP. I would be very surprised if the future weight of evidence fails to reveal such a relation. At the same time, though the authors specifically set out to test the hypothesis that BP is related to BL, NHANES was not specifically designed to test this hypothesis. Thus I would place this study somewhere between a purely hypothesis-generating and a purely hypothesis-testing study.

A true cross-sectional study, specifically designed to test the observed association of BP with BL, would be highly desirable, as would a prospective study of changes in BP in relation to changes in BL. Evaluation of other age-sex groups in the NHANES sample would also be helpful. Finally, it may be possible to determine the biologic mechanism underlying an effect of BL on BP.

Thank you for the chance to attend and comment on this interesting presentation.

cc. Dr. John O'Neil

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