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What is the meaning of non-linear dose–response relationships between blood lead concentrations and IQ?

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Abstract

Recent literature [e.g. Canfield RL, Henderson CR, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 mg per deciliter. New Engl J Med 2003;348(16):1517–1526; Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, Canfield RL, Dietrich KN, Bornschein R, Greene T, Rothenberg SJ, Needleman HL, Schnaas L, Wasserman G, Graziano J, Roberts R. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ Health Perspect 2005;113(7):894–899] has suggested the existence of a supra-linear dose–response relationship between environmental measures such as blood lead concentrations and IQ. This communication explores the mathematical requirements placed on such dose–response relationships when the environmental measure, or independent variable, is lognormally distributed and the effect, or dependent variable, is normally distributed. Results of the analyses show that a supra-linear slope is a required outcome of correlations between data distributions where one is lognormally distributed and the other is normally distributed. The analysis shows that caution should be taken in assigning biological significance to supra-linear dose–response relationships in these instances. Detailed analyses of such data sets should be conducted to determine if the magnitude of supra-linear slopes are more or less than mathematically required, and from there to consider biological significance.
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1. Introduction

Several researchers have recently reported non-linear dose–response relationships between children's blood lead concentrations and IQ. Specifically, these researchers report that the inverse association between IQ and blood lead concentrations has a steeper slope at low blood lead concentrations (i.e. below 10 μg/dL) than at more elevated blood lead concentrations, often referred to as a supra-linear slope. This pattern was noted over a decade ago by Schwartz (1994) and has been recently expanded upon in work by Canfield et al. (2003) and Lanphear et al. (2005).

Schwartz (1994) reviewed eight studies relating IQ to blood lead concentrations in young children. Some of the studies were cross-sectional and some longitudinal. IQ measurements were in school-age children, but the blood lead concentrations were at various ages, from as young as 2 years in one of the studies, to school age in others. The IQ–blood lead analysis was based on integrated exposure over 3 or 5 years for some studies, and based on single blood lead measurements for others. Schwartz found IQ–blood lead slopes of approximately −0.232 for studies with mean blood lead concentrations above 15 μg/dL, −0.323 for studies with mean blood lead concentrations below 15 μg/dL and −0.58 for a single study with a mean blood lead concentration below 10 μg/dL.

Canfield et al. (2003) examined the relationship between blood lead concentrations and IQ in 172 children, considering IQ at ages 3 and 5 years, and four measures of blood lead: the highest observed blood lead for a child (peak blood lead, typically at age 2 years), the concurrent blood lead concentration (measurement at the time of the IQ test), life-time average blood lead concentration and average in infancy, defined as 6–24 months. The authors found an inverse association between blood lead and IQ for each measure. The authors also examined the IQ–blood lead relationship in the subgroup of children whose peak blood lead concentrations were less than 10 μg/dL, and observed that for all measures, the IQ–blood lead slope was steeper, suggesting a greater loss in IQ points per dL blood lead increase in this subset of children.

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Lanphear et al. (2005) performed an analysis of pooled data from seven studies involving over 1300 children. The authors examined the relationship between blood lead and IQ, focusing largely on concurrent blood lead concentrations taken at the time of the IQ tests, which was between approximately ages 5 and 7 years in the various studies, and separately analyzing children whose peak blood lead concentrations were below versus above 10 μg/dL. The authors found an inverse association between blood lead concentration and IQ, with the steepest IQ–blood lead slope for blood lead concentrations less than 10 μg/dL.

Overall, the above studies suggest that the slope of the IQ–blood lead relationship is supra-linear at low blood lead concentrations for children, that is, the inverse association between IQ and blood lead concentrations has a steeper slope at low blood lead concentrations than at more elevated blood lead concentrations. There is no confirmed mechanistic or physiologic explanation. Nonetheless, Canfield et al. (2003) cites Bae et al. (2001) as supportive, noting Bae et al.'s conclusion that elevated metal concentrations may enhance cellular defense mechanisms, lessening the rate at which additional damage can occur, and implying that such compensatory mechanisms do not occur at lower blood lead levels. Lanphear et al. (2005) cites Lidsky and Schneider (2003), Markovac and Goldstein (1988) and Schneider et al. (2003) as also providing possible mechanistic explanations. It should be noted that all the preceding studies (other than Lidsky and Schneider (2003), which is a review article), rely on biochemical and cellular indicators in vitro as supportive of a supra-linear dose–response relationship. In contrast, in a comprehensive review article, Calabrese and Baldwin (2003) cite several studies indicative of induction of protective mechanisms (e.g. increased glutathione levels) at low lead levels, resulting in a sub-linear dose–response relationship, where sub-linear is defined as an inverse association between IQ and blood lead concentrations with a more shallow slope at low blood lead concentrations than at more elevated blood lead concentrations. While these studies are of interest, it is difficult to extrapolate, particularly from in vitro findings of a limited number of indicators, to conclusions about dose–response relationships for learning in humans. Overall, there is no convincing evidence from animal studies supporting a supra-linear dose–response for the IQ–blood lead relationship. As summarized by the Work Group of Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP, 2004):

> "The Work Group is unaware of directly relevant animal or in vitro studies that demonstrate a steeper slope for adverse effects of lead exposure at lower blood lead levels than observed at higher levels."

Thus, these findings warrant critical analysis and, in particular, an assessment of whether an alternate explanation is plausible. This communication presents a theoretical statistical analysis of the shape of the expected dose–response relationship in order to assess the extent to which the supra-linear shape is a requirement of the distributional shapes of blood lead concentration and IQ data.

2. Methods and results

For this analysis, we assume that a correlation exists between increases in blood lead concentrations and decreases in IQ. This assumption is made without regard to the existence or direction of any cause-and-effect, and without regard to the magnitude of the correlation. Certain requirements are placed on the nature of such a correlation by the statistical distributions of blood lead and IQ.

Blood lead concentrations in the general population are lognormally distributed. For example, consider the results of the National Health and Nutrition Examination Surveys (NHANES) II and III analyses (Brody et al., 1994; Pirkle et al., 1994, 1998). Blood lead concentrations of young children in individual communities are also lognormally distributed (for example, see Hogan et al., 1998). In contrast, raw scores from various IQ tests are standardized to a normal distribution, with a mean of 100 and a standard deviation of 15. (The tails of an IQ distribution deviate from normality as infinitely high or low IQs do not exist.) Typical blood lead concentration and IQ distributional shapes are shown in Fig. 1a and b. The curves displayed are theoretical and do not correspond to any particular data set, although they are consistent with typical data sets. The blood lead concentration distribution shown has a geometric mean of 8 μg/dL and a geometric standard deviation of 1.8, while the IQ distribution shown has a mean of 100 and standard deviation of 15. A blood lead geometric mean of 8 μg/dL was chosen to be approximately consistent with the median blood lead levels of the data sets analysed by Lanphear et al. (2005) and Canfield et al. (2003). Ignoring all other predictors of IQ for the moment, we can graph the relationship between blood lead concentrations and IQs by matching percentiles of the distributions shown in Fig. 1a and b (i.e. assume a child with the geometric mean blood lead concentration has the mean IQ, a child with the 95th percentile blood lead concentration has an IQ at the 5th percentile, and so on). Fig. 1c shows the resulting IQ–blood lead relationship. The dose–response relationship is obviously supra-linear. No assumptions have been made in constructing this figure other than that blood lead concentrations are lognormally distributed, IQ is normally distributed, and that the two have an inverse relationship. The supra-linear slope is a requirement of the distributional properties of blood lead and IQ.

In the example above we have assumed that changes in blood lead account for all observed variability in IQ, and that no confounders exist. Several studies of the IQ–blood lead relationship have considered the many other effects on IQ, such as parental IQ and socioeconomic status, and have attempted to control for such confounders (e.g. Lanphear et al., 2005). However, the required supra-linear nature of the IQ–blood lead relationship will not necessarily change when confounders are included in the analysis if the confounders themselves are also normally distributed (e.g. mother's IQ). A confounder analysis cannot eliminate the supra-linear IQ–blood lead slope unless the residual IQ distribution (i.e. the IQ distribution that is unexplained by anything other than blood lead) is lognormally distributed with the tail of the distribution

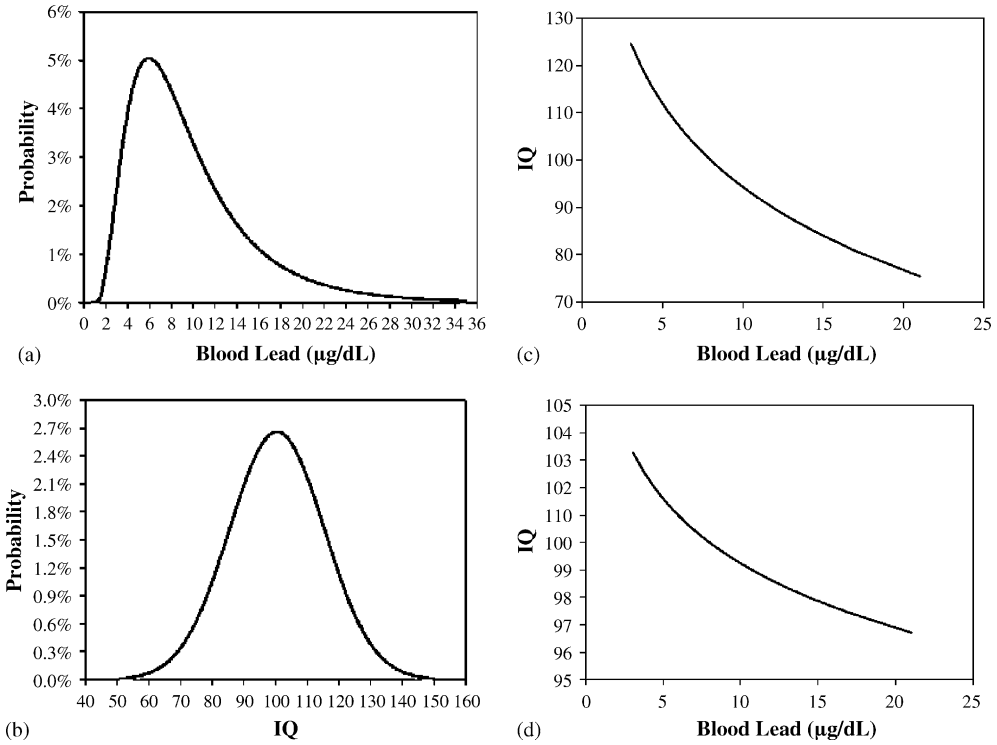

Fig. 1. (a) Theoretical curve illustrating a lognormal distribution of blood lead concentrations with geometric mean of 8 μg/dL and geometric standard deviation of 1.8. (b) Theoretical curve illustrating a normal distribution of IQ with mean of 100 and standard deviation of 15. (c) Theoretical curve resulting from an assumed inverse relationship of blood lead concentrations from (a) and IQ from (b) where values for the 50th percentiles are paired, and values from the 95th percentile are paired with the 5th percentile, etc. (d) Theoretical curve resulting from an assumed inverse relationship of blood lead concentrations and IQ where the IQ standard deviation is reduced to 2. Note vertical scale difference between diagrams (c) and (d).

towards the low IQ end. Analyses of IQ predictors conducted to date are too imprecise to be likely to yield this type of residual IQ distribution. As a result, virtually any blood lead–IQ analysis of a population of children will show the supra-linear slope as a result only of the nature of the statistical distributions. Fig. 1d shows an example IQ–blood lead relationship where the variability in IQ that is assumed to be related to blood lead is small (the standard deviation of IQ is set equal to 2 rather than 15 as in Fig. 1c). The blood lead and IQ distributions in this figure produce IQ–blood lead slopes that are comparable to those reported in the epidemiological literature summarized above. At a blood lead concentration greater than 10 μg/dL, IQ drops by about two points for every 10 μg/dL increase in blood lead. Below a blood lead concentration of 10 μg/dL, IQ drops by about six points over the 0–10 μg//dL blood lead range. The difference in IQ–blood lead slopes above and below a blood lead concentration of 10 μg/dL is about a factor of three in this example. This difference varies with the geometric standard deviation (GSD) of the blood lead distribution; for a GSD of 1.6 the factor is about two, and for a GSD of 2.3 the factor is about four. The increased slope of the dose–response curve will become most apparent below approximately the geometric mean of the blood lead data set.

3. Discussion

The statistical relationships described here are a requirement of correlations between environmental variables that are lognormally distributed and IQ, which is normally distributed. However, unlike the absolute measurement that blood lead represents, IQ results from a transformation that fits raw test scores to a normal distribution. As discussed by Kaufman (2001), one of the primary uses of IQ testing is to provide a predictor of school performance and to assess the need for intervention. There are many attributes to intelligence, which are only partly described through the IQ test. Thus, the actual distributional shape of intelligence (however characterized) in the population is unknown, and perhaps unknowable. As a result, one IQ point does not represent an absolute increment in intelligence in the same manner that 1 μg/dL of blood lead has an absolute meaning. Rather, the tests are scaled so that one IQ point represents a certain percentage of the population (Kaufman, 2001). The difference between an IQ of 89 and 90 versus the difference between an IQ of 110 and 111 represents the same percent of a ranked population, but does not necessarily represent an equal increment in intelligence. This difficulty further confounds our thinking about the biological significance of a non-linear dose–response relationship between environmental measures and IQ.

The supra-linear dose–response relationship described here will also be observed for other environmental contaminants that are negatively correlated with IQ. For example, recent publications have focused on the relationship between exposure to mercury and IQ (Trasande et al., 2005). Fig. 2 shows data for cognitive test scores adjusted for confounders versus cord blood mercury concentrations reproduced from the National Research

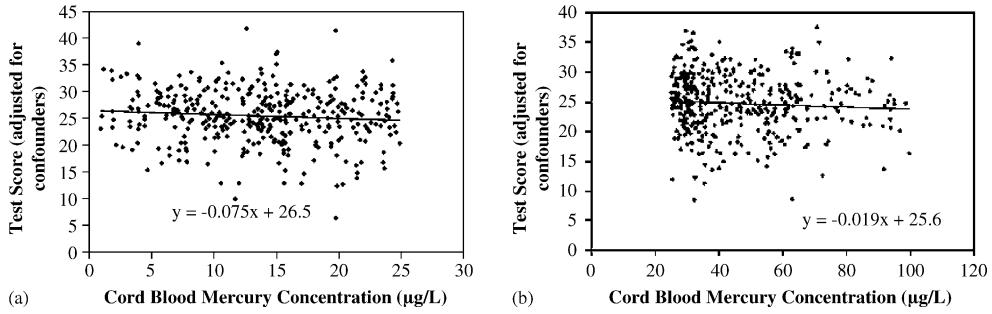

Fig. 2. (a) Test scores adjusted for confounders vs. cord blood mercury levels below 25 μg/L, from data of Budtz–Jorgensen as reported in NRC (2000). (b) Same as (a) but for cord blood mercury levels above 25 μg/L.

Council (NRC) (2000). This data set includes unpublished data points for approximately 750 children from E. Budtz-Jorgensen, University of Copenhagen, November 12, 1999, as shown in NRC (2000). The test scores have a mean of 25 and a standard deviation of 5.1 after adjustment for confounders. The cord blood mercury concentrations have a geometric mean of 24.3 μg/L and a GSD of 2.38. NRC displays the cord blood mercury concentrations on a logarithmic axis, but here we use a standard axis for ease of comparison with the blood lead–IQ graphs. NRC discusses the data in terms of estimating a benchmark dose based on various models fit to the observed dose–response relationship. We divided the data into two subsets, with cord blood mercury concentrations below 25 μg/L (the approximate geometric mean of the data set), and between 25 and 100 μg/L. (Twenty-four additional data points with cord blood mercury concentrations between 100 and approximately 380 μg/L are not plotted.) We used linear regression to fit a straight-line relationship between cord blood mercury and cognitive test scores for the two subsets of data. The test score—cord blood mercury slope is approximately −0.019 for cord blood mercury concentrations above 25 μg/L, and −0.075 for cord blood mercury concentrations below 25 μg/L, showing the expected supra-linear nature of the dose–response relationship. These slopes differ by approximately a factor of four, consistent with that predicted above for the relationship between IQ and blood lead data sets with a GSD of 2.3. The cognitive test scores in this example were adjusted by the original researchers for other predictors, supporting the discussion above that confounder adjustment will be insufficient to negate the requirement for a supra-linear dose–response slope. It is also worth noting that NRC concluded that a supra-linear dose–response relationship between biological markers of mercury exposure and cognitive effects was less plausible than other models (e.g. additive or perhaps sub-linear) and selected a modeling approach that ruled out a supra-linear dose–response relationship (NRC, 2000).

Although the supra-linear dose–response relationship described here characterizes observations over a broad range of the blood lead and IQ distributions, it would not be expected to characterize the extreme ends of the dose–response relationship between blood lead and IQ. As noted above, infinitely high IQs do not exist and as a result, the theoretical dose–response relationship will curve again as it approaches very low blood lead levels and very high IQs, lending a sigmoidal shape to the curve. If a dose–response relationship between blood lead and IQ in fact even exists in this region, it may be difficult to observe in epidemiological studies because of the limited population at the extremes of the distributions. Note that the truncation of IQ at the low-IQ end of the curve does not substantially affect the shape of the dose–response curve described here; it would simply become flat at high blood lead and low IQ levels.

In summary, one must take care when interpreting statistical relationships with unexpected results that have no apparent underlying biological or other scientific basis. This analysis shows that we should be cautious in assigning biological significance solely to the observed increase in the inverse IQ–blood lead slope at low blood lead concentrations. In this case, consistency of findings in numerous epidemiological studies is an insufficient basis for concluding that the finding is of biological significance, as all studies share a common alternative explanation. In this example, we expect to see the supra-linear IQ–blood lead slope in all such studies because it is a requirement of the shape of the blood lead concentration and IQ distributions. It is critical to re-evaluate the epidemiological studies purporting to show a supra-linear dose–response relationship, recognizing that the dose–response curve between any environmental measure that is lognormally distributed and any cognitive score that is normally distributed will by necessity have a non-linear slope. More careful analyses must be done to determine if the magnitude of the observed supra-linear slope in these epidemiology studies is more or less than expected, based on the statistical nature of the blood lead and IQ distributions. In particular, the blood lead GSD together with the shape and standard deviation of the residual IQ distribution, after correction for confounders, can be used to predict the expected shape of the dose–response curve. If epidemiological studies yield a dose–response curve that is more or less supra-linear than expected on this basis, then we can begin to form conclusions about the nature of lead toxicity at high and low blood lead concentrations, and investigate further for mechanism and/or causality.

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