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Low-Level Lead Exposure and Children's IQ: A Meta-analysis and Search for a Threshold

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To assess the strength of the association between blood lead and children's IQ, a meta-analysis of the studies examining the relationship in school age children was performed. Emphasis was given to the size of the effect, since that allows comparisons that are informative about potential confounding and effect modifiers. Sensitivity analyses were also performed. A highly significant association was found between lead exposure and children's IQ ($P < 0.001$). An increase in blood lead from 10 to 20 μg/dl was associated with a decrease of 2.6 IQ points in the meta-analysis. This result was robust to inclusion or exclusion of the strongest individual studies and to relaxing the age requirements (school age children) of the meta-analysis. Adding eight studies with effect estimates of 0 would still leave a significant association with blood lead ($P < 0.01$). There was no evidence that the effect was limited to disadvantaged children and there was a suggestion of the opposite. The studies with mean blood lead levels of 15 μg/dl or lower in their sample had higher estimated blood lead slopes, suggesting that a threshold at 10 μg/dl is implausible. The study with the lowest mean blood lead level was examined using nonparametric smoothing. It showed no evidence of a threshold down to blood lead concentrations of 1 μg/dl. Lead interferes with GABAergic and dopaminergic neurotransmission. It has been shown to bind to the NMDA receptor and inhibit long-term potentiation in the hippocampal region of the brain. Moreover, experimental studies have demonstrated that blood levels of 10 μg/dl interfere with a broad range of cognitive function in primates. Given this support, these associations in humans should be considered causal.

INTRODUCTION

A large number of recent studies have reported negative associations between lead exposure and cognitive development in children at lead concentrations once considered normal. While the negative effects of lead were not statistically significant in all of the studies, the overall impression is quite strong. This has been confirmed by a recent meta-analysis (Needleman and Gatsonis, 1990). Recent attention has focused on the evidence for IQ deficits at general population exposure levels.

The methods of meta-analysis have developed considerably since Fisher and now provide a number of options, depending on the goals of the author. Early meta-analyses of the effects of general population exposure to lead on children's IQ used Fisher's procedure or variants (Schwartz *et al.*, 1985; Needleman and Gatsonis, 1990). This procedure, which can be described as combining P values or correlation coefficients, has advantages and disadvantages. The advantages are that most studies provide enough information to allow their inclusion in the analysis, and that studies using different measures of exposure can easily be combined, since the meta-analysis is not testing for a specific exposure–response

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relationship. Hence, Needleman and Gatsonis (1990) were able to combine all studies using either blood lead or tooth lead in their meta-analyses. While they performed separate meta-analyses for blood lead and tooth lead exposure measures, their approach would have allowed the two types of studies to be combined. Their results show a consistent pattern of studies generally finding a negative correlation between lead exposure and covariate adjusted IQ. While not all individual studies were significant, many were, and the overall pattern was highly unlikely to have occurred by chance.

Chance is not the only adversary an epidemiologist faces in trying to detect reality in a hall of mirrors. All epidemiologic studies risk the possibility of confounding or bias. While a meta-analysis focused on correlation measures can speak to the issue of chance, it does not address the issue of confounding (henceforth defined broadly to include selection bias, etc.) directly. Usually, the pattern of studies varies enough in terms of population selected and the levels and correlations between potential confounders and the exposure of interest to be informative on that issue. This requires the examination of effect sizes, however.

The reason is straightforward. Suppose an omitted or imperfectly controlled covariate confounds the association that one is examining. This could produce an association that is in the same direction in each study in the meta-analysis. What looks like an overwhelming pattern is merely systematic confounding. The situation changes when one begins to focus on regression coefficients. The bias introduced into the lead IQ regression coefficient in a given study depends on the coefficient of the omitted confounder on IQ and the coefficient of the omitted confounder on lead. Unless both of these coefficients are the same in all studies, the induced regression coefficient of lead on IQ will differ, usually substantially, from study to study. Hence, the similarity of the regression coefficient or related measure of the size of an effect (e.g., an odds ratio) across studies is quite informative about the likelihood of confounding. Moreover, an analysis that focuses on measures of effect allows the examination of specific hypotheses about confounding or effect modification. If one hypothesizes that the impact of lead exposure is greater in disadvantaged populations, the studies can be stratified by that factor, and the mean regression coefficient, or IQ impact for a given change in lead exposure, can be contrasted between the groups. More sophisticated analyses can treat the regression coefficients of individual studies as data and properties of the studies as predictor variables. A metaregression, looking to see which factors are predictive of differences in results, can be performed.

Meta-analysis is particularly useful in environmental epidemiology, where one is usually examining outcomes that depend on many factors and where the environmental insult under examination is not expected to be one of the most important factors. For example, the National Academy of Sciences report on passive smoking (National Research Council, 1986) included a meta-analysis which was instrumental in changing the way people thought about the evidence. Where people once remarked that most of the studies had reported no significant association, the meta-analysis forced attention to the fact that the estimated effects of passive smoking were roughly similar across all of the studies and consistent with a significant elevated risk. What made this argument persuasive was the sensitivity

analyses that were performed and the examination of specific hypotheses that a focus on measures of effect, rather than correlations, allowed. Many critics had claimed that the results were skewed by one study showing the largest and most significant effect. Leaving out that study had little impact on the results. Others worried whether there was a difference between studies in occidental and oriental populations. The relative risks were estimated stratified by race, and similar relative risks were obtained. Another recent meta-analysis of studies examining whether indoor NO_2 exposure was associated with respiratory symptoms has recently been published (Haselblad *et al.*, 1992) and it received a positive evaluation by the Environmental Protection Agency's external Science Advisory Board. Again, the emphasis was on combining odds ratios, and sensitivity analyses were performed.

Since a meta-analysis combining correlation coefficients has already been performed for lead, and since the studies published since that analysis have generally reported negative correlations (mostly significant) between lead exposure and IQ, it is unlikely that repeating that type of analysis would produce a different result. This analysis focuses on the second type of meta-analysis, in the hopes of gaining some insight into the possibility that consistent negative correlations between lead exposure and IQ found in essentially all studies could be due to confounding.

When combining estimates of effect from multiple studies, it is usual to assign weights. Two types of weights can be used. The first set of weights weigh each study by the inverse of the estimated variance of the effect estimate. This gives studies whose estimates are less certain less weight. This type of weighting is universally accepted, although it cannot always be applied if all studies do not provide standard errors or some other method of estimating the confidence interval for the study. In addition, quality weighting schemes have been derived. In this approach, weights based on factors such as degree of control for confounding and avoidance of selection bias are assigned to studies. This approach has been criticized for being subjective. Yet classic review articles, the methodology meta-analysis seeks to replace, used a similar, although more qualitative, judgment system. Sometimes researchers outside the field are asked to blindly judge the quality of the papers. If the quality issues pertain to general epidemiologic problems, such as how the controls were selected, this can be a useful method. However, environmental epidemiology usually does not involve case–control studies and usually has continuous exposure measures and continuous covariates. The issues of how well the studies were done more often requires field-specific knowledge and knowledge of how the measurements were taken, which again relates to issues generally requiring expertise in the field. For example, a recent meta-analysis (Thacker *et al.*, 1992) restricted to the few longitudinal studies of lead reported that the highest quality ranking was assigned by their reviewers to the Sydney prospective study (Cooney *et al.*, 1989). A letter to the editor has recently clarified that this was due to a coding error, and the Boston study is actually ranked highest. Yet the Sydney study included some children whose blood lead levels were only assessed by finger stick. The Boston study used finger sticks up through age 18 months and subsequently used venipuncture. The finger stick method for lead assessment is well known to be prone to surface contamination

and to be both upward biased and more noisy. Careful attention to this issue would lead one to assign a lower weight to studies from Boston using blood lead concentrations obtained before age 2 years than to studies from Boston using blood lead levels obtained at age 2 and later, but this does not appear to have been done. This is likely because the rankers were less familiar with the issue.

Another problem with quality weighting schemes commonly used today is that they have been developed for general epidemiology. In most areas of epidemiology, the outcome measures are dichotomous, and the exposure measures are often dichotomous. The issues given priority in general schemes reflect this. More specific weighting schemes for continuous multifactorial outcomes and continuous measures need to be developed for environmental epidemiology, and papers need to report those criteria. The use of continuous models in environmental epidemiology makes the inferences more model dependent than in other fields, and statistical issues of model assessment where relationships are continuous and potentially nonlinear need to be given more weight. Collinearity raises other issues. For example, the advantage of an experimental paradigm is that random allocation of treatment generally eliminates any correlation between treatment and covariates. Environmental epidemiology studies that select populations where the correlation between exposure and covariates is minimized should therefore be given considerably higher weight (unless the process involves selection bias). Such a study design improves power, since it is the variation in lead independent of all other covariates that are correlated with IQ, for example. It also reduces the likelihood of confounding. If a covariate is not correlated with an exposure, it will not confound the exposure. In this regard, the Boston prospective lead study probably has the lowest amount of variation in blood lead explained by the covariates, although enough information is not available in the published papers to definitively conclude this and hence to assign weights on this criteria.

The approach used in this study is to weight by the inverse of the variances. Because the true slope may actually vary between populations, it is usual to fit a random effects model (DerSimonion and Laird, 1986), and this study adopts that method. Once a basic meta-analysis has been done, sensitivity analyses are done to contrast results across studies that differ on key factors that are potential confounders, to see if there is any indication of confounding.

DATA AND METHODS

The studies examined in this meta-analysis are studies relating blood lead to full-scale IQ in school age children. Blood lead is chosen as the exposure measure because it is the measure most commonly available and the measure that public policy measures are based on. Full-scale IQ in school age children was chosen as the outcome for several reasons. IQ is again an outcome that has received the most public policy attention—it is the outcome measure of interest. Full-scale IQ is chosen because it is always reported and because its use avoids issues of which subscale is more relevant for lead exposure. IQ in school age children is chosen, rather than some earlier measure, such as Bayley Scales, because it is much more

stable and much more predictive of future outcome. Both longitudinal and cross-sectional studies relating IQ to blood lead are examined. Both study designs examine the same hypothesis; the difference is one of methodology. The longitudinal studies clearly can tell us more about critical periods of exposure, etc. Whether there is a systematic difference between what they tell us about the relationship between blood lead and IQ and what the cross-sectional studies say will be examined in the analysis. The studies that met the major criteria (full-scale IQ in school age children, with blood lead as the exposure index) are shown on Table 1. They include four cross-sectional studies and three longitudinal studies that have reported results for school-age children. In addition, the longitudinal study of Silva and co-workers (1988) is listed as a cross-sectional study, because the lead analysis was conducted cross-sectionally.

For the cross-sectional studies blood lead was only measured once, and that measure was used. The longitudinal studies present a choice, since analyses are usually presented using several alternative exposure measurements. The studies themselves did not provide a clear pattern for which exposure was the best. This is not surprising since all of the postnatal exposure levels are correlated. To make the choice, some attention was paid to the neurotoxicological literature. The neural network in the brain is most plastic during the first 3 years of life, and there is considerable evidence that basic cognitive abilities develop in that period. There is also evidence that lead may modify the formation of the neural network, both indirectly, by interfering with neurotransmission through several demonstrated mechanisms, and more directly, by effecting neural cell adhesion molecules and NMDA receptor functioning. This suggests that a measure during that period be chosen. Even if that is not the mechanism of lead toxicity, the greater plasticity of the brain in the early years suggests an emphasis on that period. This analysis uses the blood lead at 24 months for the Boston prospective study. For the Cincinnati prospective study, the integrated blood lead up to 3 years of age is chosen. For the Port Pirie study prospective study, the integrated exposure to 3

TABLE 1
STUDIES INCLUDED IN THE META-ANALYSIS

Study	Effect[a]	SE	Design[b]	Parental IQ	HOME score	Status[c]	*N*	Mean BL
Hawk *et al.* (1986)	2.55	1.5	0	Yes	Yes	Low	75	21
Hatzakis *et al.* (1987)	2.66	0.7	0	Yes	Yes	Average	509	23
Fulton *et al.* (1987)	2.56	0.91	0	Yes	Yes	Average	501	12
Yule *et al.* (1981)	5.6	3.2	0	No	No	Low	166	13
Bellinger *et al.* (1992)	5.8	2.1	1	Yes	Yes	High	147	6.5
Dietrich *et al.*	1.3	0.9	1	Yes	Yes	Low	231	15
Baghurst *et al.* (1992)	3.33	1.46	1	Yes	Yes	Average	494	20
Silva *et al.* (1988)	1.51		0	No	No	Average	579	11

[a] Estimated loss in IQ for an increase from 10 to 20 μg/dl in blood lead.
[b] 0, cross-sectional; 1, longitudinal.
[c] Low, disadvantaged; average, normal; high, advantaged.

years is also used. For the Boston study, the 24-month blood lead had the strongest association; however, for the Cincinnati and Port Pirie studies, the integrated blood lead up to 5 years had stronger associations than the ones chosen for this analysis.

Some of the studies have used blood lead directly as their index of exposure, and some have used the natural logarithm of blood lead. Few of the studies made that choice based on an assessment of which functional form best described the relationship between lead and IQ in their data. To put the studies on the same basis for comparison, the measure of effect use will be the predicted change in full-scale IQ as blood lead increases from 10 to 20 μg/dl. This is a range of exposure that occurred in all of the studies, with a reasonable number of observations. The other columns in Table 1 indicate whether parental IQ was controlled for, whether HOME score was controlled for, whether it was longitudinal or cross-sectional in design, whether the study population was predominantly disadvantaged, middle class, or advantaged, and the mean blood lead level of the children in the study. The results of the meta-analysis are then compared and contrasted with respect to those factors.

One principal concern about the relationship between blood lead and IQ has been whether there was any evidence for a threshold. This can be tested in a meta-analysis by contrasting studies with different mean blood lead levels. The reason is straightforward. Figure 1 shows a plot of a hypothesized threshold

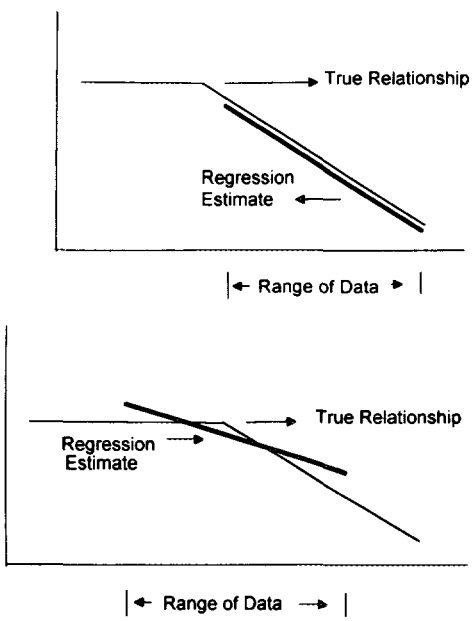

FIG. 1. A hypothesized threshold in the relationship between full-scale IQ and blood lead and the implications for the estimated regression coefficient of estimating a linear regression, using data in different exposure ranges. Note the decrease in expected slope as the range of exposures becomes lower.

relationship between blood lead and IQ in two cases. In the top panel, all of the data is above the threshold. There, the expected regression slope (shown as a heavy line) is the true slope above the threshold. In the bottom figure, most of the data is below the threshold. The expected slope from performing a regression in this data is lower, since it is the average of zero (from the data below the threshold) and the true above-threshold slope. Hence, if a threshold exists in the range of exposures covered by the available studies, one would expect the estimated slope to decrease as the mean blood lead in the study decreased. This can be examined both analytically and graphically in the meta-analysis. As a further test of this, the data from the Boston prospective lead study is examined in more detail to look for a threshold. The Boston study was chosen because it had the lowest mean blood lead level and should be most informative about a threshold. First full-scale IQ was regressed against age, race, a children's stress score, HOME score, maternal IQ, father's educational level, mother's educational level, father's occupational status, mother's occupational status, mother's time working outside the house, marital status, gestational age, birth weight, mother's drinks per week during pregnancy, otitis media history, birth order, and Hollingshead four-factor SES scale. The residuals of that regression were saved. Blood lead at 24 months was regressed against the same variables, and the residual variation in blood lead that was not correlated with any other factors was also saved. Then a nonparametric smoothed curve was fit to the relationship between the two sets of residuals. This shows the adjusted relationship between full-scale IQ and blood lead. A nonparametric smoother is a technique to estimate the dependence of a response variable as a function of an explanatory factor. It is capable of estimating nonlinear dependencies, and a threshold is one type of nonlinearity. Most smoothers are generalizations of weighted moving averages. These predict the expected value of Y at X_i as the weighted mean of the actual values of the Y's corresponding to all of the X's in a symmetric neighborhood around X_i. The weights decline with distance from the center of the neighborhood. The properties of smoothers have been extensively discussed (Härdle, 1991, Hastie and Tibshirani, 1992). LOESS, a robust, local, nonparametric smoother, was used in this analysis (Cleveland and Devlin, 1988).

RESULTS

The study of Silva *et al.* (1988) did not report a regression coefficient with blood lead, since tooth lead was a better predictor in a correlation analysis. It was possible to estimate a regression coefficient from the correlation coefficient. However, no standard error could be estimated, and the correlation coefficient was unadjusted for covariates. Hence that study was not used in the primary analysis, where inverse variance weighting was required. It was considered in the sensitivity analyses. In the baseline meta-analysis using the seven remaining studies, the estimated decrease in IQ for an increase in blood lead from 10 to 20 μg/dl was 2.57 IQ points, with a standard error of ±0.41 IQ points. Figure 2 shows a plot of the estimated IQ loss and 95% confidence intervals for the seven studies. While all of the studies did not report the correlation between blood lead and socioeconomic status, the ones that did report show that the studies cover a wide range of

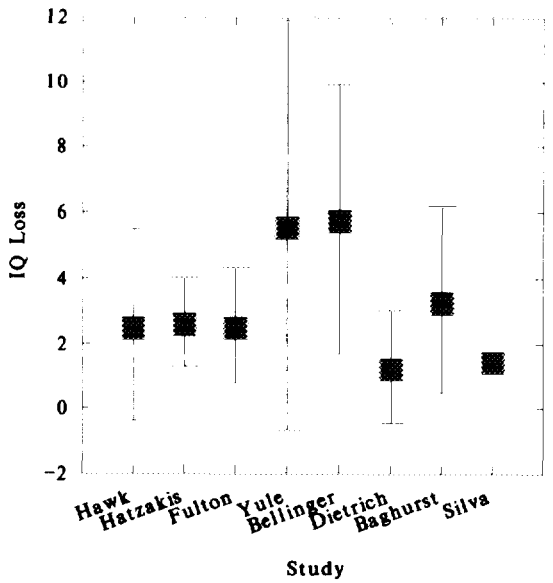

FIG. 2. The estimated loss in full-scale IQ from an increase in blood lead from 10 to 20 μg/dl, from the studies in the meta-analysis. The 95% confidence interval is also shown.

correlation. The correlation ranges from −0.193 in the Bellinger *et al.* (1992) study to 0.01 in the Silva *et al.* study, to 0.15 in the Fulton *et al.* (1987) study, and to 0.40 in the Hawk *et al.* (1986) study. Hence, if omitted socioeconomic factors were confounding this association, we would expect to see a quite wide range of variation in the induced lead coefficient.

Contrasts and Sensitivity Analyses

If the study with the largest estimated effect size is excluded (Bellinger *et al.*, 1992), there is little change in the estimated effect of blood lead on IQ (2.43 ± 0.34 IQ points). Similarly, excluding the study with the most significant finding (Hatzakis *et al.*, 1987) also had little impact on the estimate (2.52 ± 0.58 IQ points). Hence the results do not appear to be dominated by any individual study. If the study of Silva and co-workers (1988) is to be included, inverse variant weighting must be dropped. Including that study, and assigning all studies equal weight, the estimated effect is 3.16 ± 0.60 IQ points.

A further measure of the robustness of the result can be obtained by asking what would happen if new studies were published which reported no association at all between blood lead and children's IQ. To test this we examined what would happen if eight studies with an estimated magnitude of effect 0, and with the average weight of the baseline studies, were added to the analysis. That would still leave a highly significant association ($P < 0.01$) between blood lead and children's IQ, although the estimated change in IQ would be reduced by about 50%.

For longitudinal studies, the estimate IQ loss was 2.96 IQ points (±1.25 IQ points), and for the cross-sectional studies, the estimated IQ loss was 2.69 IQ

points (±0.51 IQ points). Hence there was little evidence that the two study designs were showing different effects. For studies in disadvantaged populations, the estimated IQ loss was 1.85 IQ points (±0.92 IQ points) versus a 2.89 IQ point loss (±0.50 IQ points) in the nondisadvantaged populations.

The next set of sensitivity analyses examined the effect of relaxing our criteria for study selection. There were two studies that used blood lead as the exposure index, but did not meet our criteria of examining school-age children. The study of Schroeder and co-workers (1985) was a cross-sectional examination of children of mixed ages, including some school-aged children and some younger children. The study of Ernhart and colleagues (1989) examined children in their fourth year. Both were in disadvantaged populations. Adding those studies to the seven in the baseline analysis yields an estimated mean IQ loss of 2.39 ± 0.31 IQ points. A regression coefficient was estimated from the incremental R^2 reported in the Ernhart *et al.* (1989) paper.

In studies with mean blood lead levels of 15 μg/dl and lower, the estimated effect size was 3.23 (±1.26) IQ points versus 2.32 (±0.40) IQ points in studies with mean blood lead levels above 15 μg/dl. This is confirmed in Fig. 3, which shows the estimated IQ loss for each of the seven baseline studies plotted versus the mean blood lead in the study population. If anything, a trend toward a higher slope at lower blood lead concentrations is seen.

When the residuals of full-scale IQ were smoothed against the residuals of blood lead from the Boston prospective lead study, no evidence of a threshold was seen. This is seen in Fig. 4. An approximately 7-IQ-point drop was seen over the range of blood lead residuals below 0. A residual of 0 correspond approximately to the mean blood lead level in the study, which was about 6.5 μg/dl. Hence the asso-

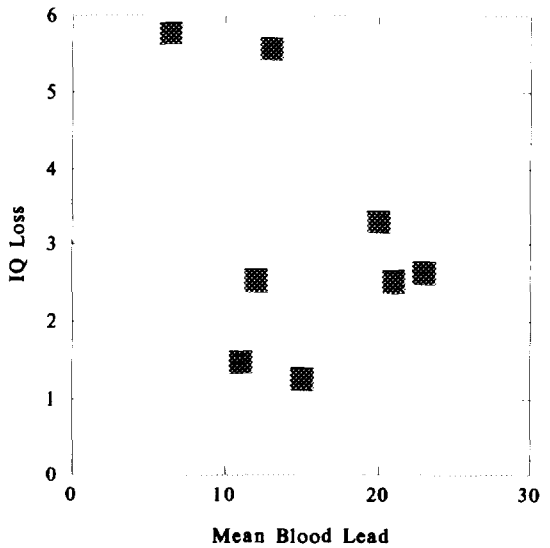

FIG. 3. The estimated impact on IQ of a 10 μg/dl increase in blood lead plotted versus the mean blood lead level in each study. A trend toward higher slopes at lower mean blood lead levels is evident.

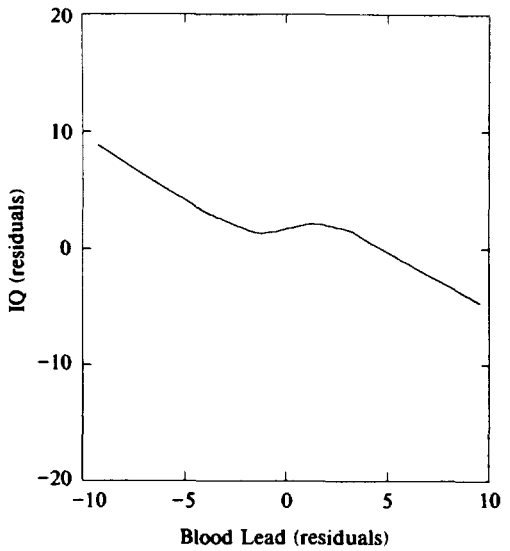

FIG. 4. The nonparametric smoothed curve of the residuals of full-scale IQ at age 10 versus the residuals of blood lead from the Boston prospective lead study. The data have been adjusted for age, race, stress, HOME score, maternal IQ, father's educational level, mother's educational level, father's occupational status, mother's occupational status, mother's time working out of the house, marital status, gestational age, birth weight, mothers alcohol use during pregnancy, otitis media history, birth order, and Hollingshead four-factor SES scale.

ciation between blood lead and IQ clearly continues at blood lead levels below 5 μg/dl in this study.

DISCUSSION

A highly significant association is seen between blood lead levels and full-scale IQ in school-aged children. The association is significant in most of the individual studies and relatively consistent in effect size. The roughly similar effect sizes seen in the studies argues against the possibility of inadequate control for covariates, although it can never completely resolve that issue. The results were reasonably robust, since excluding of the most significant study or the study with the largest effect size gave similar results. An unweighted analysis gave a somewhat higher estimate of effect, but again was not significantly different. This indicates that the results are not due to one study with a high weight. Most significantly, even eight new studies that found no association at all between blood lead and children's IQ would not disturb the conclusion that overall the evidence strongly supports a significant association between blood lead and children's IQ.

In addition, the results from the longitudinal and cross-sectional studies, taken separately, were quite similar. This is reassuring since it supports the decision to combine both study designs, and since the two studies designs differ in the types of potential problems they might be expected to encounter. The longitudinal designs must contend with potentially nonrandom loss to follow-up, while the cross-sectional designs have poorer ascertainment of exposure, for example. A recent

paper has noted that the longitudinal studies are less consistent when examining results at earlier ages (Thacker *et al.*, 1992). The greater consistency in looking at full-scale IQ in school-age children and the consistency of the longitudinal studies with the cross-sectional studies suggest that the use of this outcome is important for epidemiologic as well as public policy reasons. As Thacker and co-workers (1992) have pointed out, the sample sizes of the longitudinal studies were not large, and their power was subsequently not great. The use of a more stable outcome measure such as IQ in school-age children has considerable advantage in such circumstances.

A particularly interesting finding was the suggestion that the IQ loss is lower in the studies looking at disadvantaged children. There are several possible explanations for this finding, which deserve further examination. First, the difference could reflect a real difference in sensitivity to lead. It is possible that the effects of lead are muted in children who have already had their higher order functioning disturbed by other factors. That is, the more basic functioning may be more resilient to factors like lead. Supporting this hypothesis is the possibility (discussed below) that the effect of each incremental increase in lead exposure diminishes. If other factors have already impaired the cognitive pathways most sensitive to lead, there may be a true subadditive effect of lead and these other disturbances.

Alternatively, the observation may be an artifact of a well-known epidemiologic phenomena. It is much more difficult to discern the effects of a minor factor in a particular outcome in a population with high but variable exposure to many more important factors. It is much easier to see the impact in a very clean population. This is well known in the field of air pollution epidemiology, where almost all studies have sought to focus on never smoking populations. No questionnaire will ever obtain good enough information on smoking to perfectly control for it, and the uncontrolled for variation in smoking can mask or artificially enhance the effect of air pollution. This has been demonstrated empirically. Chestnut *et al.* (1991) and Schwartz (1989) have both reported associations between air pollution and lung function in never smokers, but not in smokers, for example. And Comstock *et al.* (1985) reported a weak association between indoor exposure to gas stoves and chronic respiratory symptoms. A reanalysis (Helsing *et al.*, 1982) restricted to persons unexposed to tobacco reported a much stronger association.

Disadvantaged populations may have a much lower signal to noise ratio and a much greater chance of confounding. Hence studies, such as that of Bellinger and co-workers (1992), may represent the best opportunity to examine the adverse health effects of lead.

The finding that the slope of the blood lead–IQ relationship may be higher in studies with lower exposures to lead is also of considerable interest. Given the high slopes found in the studies with mean blood lead levels below 15 μg/dl, it seems quite implausible that a threshold could exist in those studies at 10 μg/dl. Indeed, it is the opposite hypothesis that now deserves serious consideration. Figure 3 indicates that the slope of the IQ–blood lead relationship may well increase with decreasing mean blood lead level across the entire range of the studies. This would suggest that a logarithmic dose–response relationship may indeed

be appropriate. There are toxicological effects that show saturation phenomena, and there are complex feedback control mechanisms in the human body, often with a series of feedbacks that cut in as homeostasis becomes more disturbed. This makes such a finding plausible. If in fact the slope increase at lower blood lead levels, this will have substantial public policy implications. Measures that reduce background exposure will become quite important if this is the case. Further examination of this issue and more studies at low blood lead concentrations (and in advantaged populations) are clearly warranted.

The direct examination of the Boston study clearly shows evidence of a relationship well below 7 μg/dl, with no evidence of a threshold. This is not the first report of such a finding. A recent reanalysis of the data of Needleman *et al.* (1979) reported that a similar nonparametric smooth of adjusted full-scale IQ versus dentine lead levels showed no evidence of a threshold down to concentrations of 1 ppm (Schwartz, 1993). That is a very low dentine lead level.

In summary, the studies published since the Needleman and Gatsonis (1990) meta-analysis have, as a group, only strengthened the general conclusion that lead is negatively associated with cognitive performance. Studies of associations between lead and IQ in school-age children show considerable consistency in estimated magnitude of effect across a range of study designs, continents, and populations, which suggests that the observed association is unlikely to be due to omitted variable bias or imperfect covariate control. The meta-analysis is robust and indicates there is no evidence for a threshold. This conclusion is supported by a more detailed reexamination of the data from the Boston study.

There is a considerable toxicological data showing that lead interferes with dopamine neurotransmission (Cory-Slechta and Widzowski, 1991) and with the NMDA receptor (Alkondon *et al.*, 1990). This pathway has been hypothesized to be critical for learning processes. Paralleling this finding are results showing low-level lead exposure inhibits long-term potentiation in the hippocampal region of the brain (Lasley *et al.*, 1991; Weigand *et al.*, 1991). There is also evidence that lead inhibits the regulation of the neural cell adhesion molecule, resulting in impaired learning (Regan, 1991). Lead has also been shown to interfere with various other neurotransmitters (Silbergeld, 1992). Picomolar concentrations of lead also significantly activate protein kinase C (Markovac and Goldstein, 1988) and have been shown to generally interfere with calcium second messenger systems which regulate neurotransmission.

Studies in primates have also documented disturbances in cognitive functioning at relatively low blood lead levels. For example, monkeys with average blood lead levels of 11 or 13 μg/dl showed, at age 3, significant decrements on discrimination reversal tasks. These are tasks where a monkey, having learned to, e.g., always choose the red object, must relearn the paradigm and always choose the blue (Rice, 1985). Distracting stimuli had a greater effect on lead-treated monkeys. Other deficits in learning were also observed in monkeys at these blood lead levels (Rice, 1992). These are experimental protocols, with no confounding by omitted variables to worry about. In the light of this evidence, it is only reasonable to assume the strong epidemiologic association found in the meta-analysis is causal.

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