Declining Blood Lead Levels and Changes in Cognitive Function During Childhood

The Port Pirie Cohort Study

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Context.—Many studies have found a significant inverse association between early exposure to environmental lead and cognitive function in childhood. Whether these effects are reversible when exposure is reduced is not clear.

Objective.—To assess the reversibility of the apparent effects of lead on cognitive abilities in early childhood by testing whether declines in blood lead concentrations beyond the age of 2 years are associated with improvements in cognition.

Setting.—Urban and rural communities surrounding a large lead smelter in Port Pirie, South Australia.

Participants.—A total of 375 children followed up from birth to the age of 11 to 13 years.

Design.—Long-term prospective cohort study.

Main Outcome Measures.—The Bayley Mental Development Index at age 2 years, the McCarthy General Cognitive Index at age 4 years, and IQs from the Wechsler Intelligence Scale (revised version) at ages 7 and 11 to 13 years.

Results.—Mean blood lead concentrations in the children decreased from 1.02 µmol/L (21.2 µg/dL) at age 2 years to 0.38 µmol/L (7.9 µg/dL) at age 11 to 13 years, but cognitive scores in children whose blood lead concentration declined most were generally not improved relative to the scores of children whose blood lead levels declined least. Changes in IQ and declines in blood lead levels that occurred between the ages of 7 and 11 to 13 years (r = 0.12, P = .09) suggested slightly better cognition among children whose blood lead levels declined most.

Conclusion.—The cognitive deficits associated with exposure to environmental lead in early childhood appear to be only partially reversed by a subsequent decline in blood lead level.

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DURING THE PAST 25 years there has been concern about the potential effects of environmental lead on childhood development. In the late 1970s and early 1980s, cross-sectional studies examined whether exposure to environmental lead at levels previously believed to be innocuous affects neuropsychological development.1-9 Many studies have found a significant inverse association between exposure measures and neuropsychological performance.1-7 Although the findings were not entirely consistent, most found an inverse association between exposure measures and neuropsychological performance.1-7 To test this hypothesis and address the limitations of cross-sectional studies, cohort studies were subsequently conducted in several countries. These studies collected information on critical features of lead exposure, such as the timing and extent, together with many other socioenvironmental factors that may confound the relationship between lead exposure and neuropsychological development. Most,10-13 but not all, cohort studies14,17 found a significant inverse association between early exposure to environmental lead and cognitive functioning in childhood after adjustment for confounding factors. A question with important public health ramifications is whether the apparent deleterious effect of early-life exposure to lead is reversed when, later in childhood, exposure is reduced. Such exposure reduction could occur either by environmental management or as a consequence of the decreased absorption that appears to accompany growth.

Recently, Ruff and colleagues16,19 reported that decreases in blood lead level were associated with cognitive improvements in children aged 13 to 87 months. Participants in their study all had initial blood lead levels between 1.21 and 2.66 µmol/L (25 and 55 µg/dL) and reductions were achieved with the chelating agent calcium sodium EDTA. However, the question of whether changes in blood lead levels in individuals are associated with changes in cognition has not been examined in any long-term cohort study. The Port Pirie Cohort Study commenced in 1979. The geometric mean blood lead concentration of the children in this cohort increased from 0.40 µmol/L (8.3 µg/dL) at birth to 1.02 µmol/L (21.2 µg/dL) at age 2 years and decreased to 0.38 µmol/L (7.9 µg/dL) by the age of 11 to 13 years. In previous studies, we reported that exposure to lead in this cohort was inversely associated with cognitive performance at ages 2, 4, 7, and 11 to 13 years, and that this association was still apparent after adjustment for a wide range of confounding factors.17,20-22 While these findings are strongly suggestive that any causal effect of lead on cognitive abilities persists throughout the primary school years, it is nevertheless conceivable that 1 or more (unidentified) confounding factors affected the relationship between lead exposure and developmental measures at all ages.

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This article pursues an alternative approach to the assessment of reversibility by examining the relationship between individual changes in blood lead concentrations and individual changes in measures of cognitive development during the life of the cohort.

METHODS

Details of the research design have been reported elsewhere and are summarized in Figure 1.15-20 All women living in Port Pirie, South Australia (site of one of the largest lead smelting facilities in the southern hemisphere), or in the immediately adjoining region who were enrolled for antenatal care between May 1979 and May 1982 were advised by their physicians of the purpose and procedures of the study and were encouraged to contact the study coordinator (a community health nurse) to discuss participation. The study was approved by the University of Adelaide Research Ethics Committee, Adelaide, Australia, and written consent was obtained from the parents or guardians of all participating children.

Sample

The initial study population was composed of an estimated 90% of all pregnancies in and around Port Pirie during a 3-year period from 1979 to 1982. Of the resulting 723 singleton live births, 601 were assessed at age 2 years, 548 at age 4 years, 494 at age 7 years, and 375 at age 11 to 13 years. The majority of children lost to follow-up were in families that either left the Port Pirie area or could not be contacted despite intensive efforts, while a small number of families simply discontinued their participation. Potential for selective losses of participants to bias the study findings was evaluated throughout the study. The results showed that the correlation between lead exposure and early measures of cognitive development was slightly stronger in those children lost to follow-up than in those remaining in the cohort. Therefore, any differential loss to follow-up is likely to have resulted in an underestimation of the lead-cognition relationship.20

Procedures

As many as 3 venous blood samples were collected from each mother before delivery. A further sample was collected from the umbilical cord at birth, and capillary blood samples were obtained from each child at the ages of 6, 15, and 24 months, and annually thereafter until age 7 years. At age 11 to 13 years, a trained community nurse collected a venous blood sample from 326 of the 375 children still in the cohort. At the time of each blood sampling, a structured interview was conducted to obtain information on a wide range of psychosocial, demographic, environmental, and biometric factors. The adequacy of capillary sampling was tested in a prestudy trial in which both venous and capillary blood samples were collected simultaneously from 47 children. The estimated Spearman rank correlation coefficient for the 2 sampling methods was 0.97.15 Compliance with the capillary sampling protocol was monitored throughout the study.

Measures

The children’s developmental status was assessed using the Bayley Scales of Infant Development at age 2 years,23 the McCarthy Scales of Children’s Abilities at age 4 years,24 and the revised version of the Wechsler Intelligence Scale for Children at ages 7 and 11 to 13 years.25 The Bayley Scales of Infant Development are applicable to children aged 30 months or younger and yield 2 standardized scores, the Mental Development Index and the Psychomotor Development Index. Only Mental Development Index scores were used in the analysis presented herein. The McCarthy Scales of Children’s Abilities, which can be used in children 3 to 7 years old, consist of 5 scales: verbal, perceptual performance, quantitative, memory, and motor. The first 3 of these scales are combined to form the General Cognitive Index. The revised version of the Wechsler Intelligence Scale for Children, a test of general intelligence developed for use with children aged 6 to 16 years, was used to assess the cognitive abilities of each child at ages 7 and 11 to 13 years. At ages 2, 4, and 7 years, all children were assessed by a single research psychologist who was unaware of each child’s lead exposure status. At age 11 to 13 years, the subjects were evaluated by a single trained examiner who had not participated in earlier phases of the cohort study and who was unaware of the children’s exposure and developmental histories.

Blood lead concentration was measured in the Department of Chemical Pathology at the Adelaide Women’s and Children’s Hospital, Adelaide, Australia, by electrothermal atomization atomic absorption spectrometry.20 Throughout this study, both internal and external quality-control procedures were used, with consistently satisfactory results. A certified commercially prepared product was used to monitor intrabatch accuracy and ensure interbatch standardization. The coefficient of variation for blood lead measurements was 5.7% or less. External quality control was maintained by participation in 3 major programs: the National Quality-Control Program conducted by the Standards Association of Australia, Sydney, and the international programs run by the Health Department of Pennsylvania, Philadelphia, and Wolfson Research Laborato-
tory, Birmingham, England. Estimates of blood lead concentration were standardized to a packed-cell volume of 50% for umbilical cord blood and 35% for all other samples.

Ancillary variables potentially capable of confounding the relationship between lead exposure and cognitive development included parents’ occupational prestige, which was assessed using the Daniel Scale of Prestige of Occupations in Australia (lower scores indicate more prestigious jobs, which are generally associated with higher socioeconomic status); the caregiving environment, which was measured with the Home Observation for Measurement of the Environment (HOME) inventory; and maternal intelligence, which was assessed using the Wechsler Adult Intelligence Scale. Other information collected included family size and functioning scores; maternal general health status and age at delivery; parental smoking habits, marital status, and education; and child’s sex, age, grade in school, birthweight, birth rank, feeding method during infancy, duration of breast-feeding, major life events, and prolonged absences from school for any single school term during the past 5 years.

**Analytic Strategy**

Statistical analyses were performed on the natural logarithm of the blood lead concentration, and all reported mean values are geometric. To calculate lifetime average blood lead concentrations, a plot of blood lead concentration against age was constructed for each child. The lifetime average blood lead concentration up to a particular age for each child was estimated by dividing the area under the child’s curve by the specified age.

Two approaches were used to examine whether the children’s cognition improved as their lead exposure decreased. First, the relationship between blood lead concentration and cognitive function was assessed (using multiple regression models to adjust for potential confounding factors) at various ages. The covariates included in these models were child’s sex, birthweight, birth rank, feeding style during infancy, duration of breast-feeding, maternal IQ, maternal age at child’s birth, socioeconomic status, HOME score, parental smoking habits, and whether the parents lived together or apart. Second, analyses of variance were used to determine whether changes in cognitive scores were associated with decreases in blood lead concentration across the interval between any pair of developmental assessments. For each comparison, 3 groups were formed on the basis of the tertiles of decrease in blood lead concentration across that interval. In comparing scores at ages 7 and 11 to 13 years, simple differences in Wechsler IQ scores obtained at both ages were used. For all other comparisons, the developmental scores were first transformed to 2 scores to take into account variations in the estimated means and SDs of the various developmental measures used at each age.

**RESULTS**

Regression analyses for each specific developmental outcome measure revealed significant inverse associations between blood lead concentration and cognitive development at all ages, as previously described. Simple plots of the covariate-adjusted differences in developmental scores for the 3 exposure groups defined by the tertiles of lifetime average blood lead concentration at age 2 years (the age at which the children’s developmental status was assessed for the first time) also indicated that the children with greater exposure continued to perform less well at older ages (Figure 2).

However, neither of these analyses provides definitive evidence that the effect of early lead exposure persists throughout childhood. The possibility of residual confounding and/or an unidentified bias affecting all the measure-specific analyses similarly cannot be excluded, and the parallel behavior of the 3 groups identified in Figure 2 may reflect little more than a “tracking” in lead exposure. In Table 1 it is readily apparent that many children with high blood lead levels at age 2 years still had high blood lead level ranking at age 11 to 13 years, even though the overall mean exposure level decreased as the children grew older.

We therefore performed an additional analysis on the changes in cognitive

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**Table 1.—Geometric Mean Blood Lead Concentrations in μmol/L [μg/dL] at Different Ages by Tertile of Lifetime Average Blood Lead Concentration at Age 2 Years**

<table>
<thead>
<tr>
<th>Blood Lead Group</th>
<th>Age, y</th>
<th>Lower (n = 109)</th>
<th>Middle (n = 108)</th>
<th>Higher (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Lower (n = 109)</td>
<td></td>
<td>0.60 (0.06)</td>
<td>0.64 (0.06)</td>
<td>0.57 (0.06)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[12.5 (1.2)]</td>
<td>[13.3 (1.2)]</td>
<td>[11.9 (1.2)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[113.3]</td>
<td>[112.5]</td>
<td>[109.9]</td>
</tr>
<tr>
<td>Middle (n = 108)</td>
<td></td>
<td>0.89 (0.05)</td>
<td>0.94 (0.05)</td>
<td>0.85 (0.06)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[18.5 (1.1)]</td>
<td>[19.5 (1.1)]</td>
<td>[17.6 (1.2)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[109.9]</td>
<td>[107.3]</td>
<td>[104.2]</td>
</tr>
<tr>
<td>Higher (n = 109)</td>
<td></td>
<td>1.25 (0.05)</td>
<td>1.26 (0.06)</td>
<td>1.10 (0.06)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[25.9 (1.1)]</td>
<td>[26.0 (1.2)]</td>
<td>[22.8 (1.2)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[106.7]</td>
<td>[103.6]</td>
<td>[101.4]</td>
</tr>
</tbody>
</table>

*Standard deviations are multiplicative; data are geometric mean (SD), with mean scores of developmental tests in each group included in brackets. Children’s developmental status was assessed using the Bayley Mental Development Index at age 2 years, the McCarthy General Cognitive Index at age 4 years, and the Wechsler Intelligence Scale for Children at ages 7 and 11 to 13 years.
development in relation to the changes in blood lead concentration for each individual in the study. If the alleged effect of lead exposure on cognitive performance was systematic, cognitive performance might be expected to improve most among those children whose blood lead levels declined most in later childhood. On the other hand, if the lead effect is persistent, children's performance would not be expected to improve as their exposure declined.

The children's IQ at age 11 to 13 years (mean score, 100; 95% confidence interval, 98.8-101.2) was generally lower than at age 7 years (mean score, 104.7; 95% confidence interval, 103.5-106.0). There was a weak ($P = .45$) trend suggesting that children experiencing the greatest decline in lifetime average blood lead concentration from age 7 years to age 11 to 13 years exhibited the smallest decrease in IQ scores (Table 2).

Similar analyses of the change in $z$ scores from age 2 years to age 11 to 13 years and from age 4 years to age 11 to 13 years provided no evidence that the cognitive function of the children whose lead exposure declined most in those age ranges had significantly improved (Table 3).

Analyses on the ungrouped data found that correlations between changes in blood lead levels and cognitive functioning were generally weak and not statistically significant. The strongest association was between the changes in IQ and declines in blood lead levels that occurred between ages 7 and 11 to 13 years ($r = 0.12$, $P = .09$). This was weakly suggestive of a slight "recovery" among the children whose blood lead levels declined most.

**COMMENT**

Determination of the course of the cognitive effects of low-level lead exposure is an important issue because the ramifications of potential effects of lead exposure for regulatory policy depend not solely on the extent of the initially observable effects per se, but also on their persistence over time. To our knowledge, this is the first attempt to systematically relate changes in blood lead concentration throughout childhood to changes in measures of cognitive functioning in a long-term cohort study.

Our analysis shows that, compared with children with lower exposure levels, the cognitive deficit in the group with higher exposure changed little with age, even though blood lead levels declined substantially after age 2 years. It might be argued that the consistency of the association between lead exposure and cognitive development at all ages is an artifact of some insufficiency in measuring confounders at all ages or, alternatively, that it reflects a persistent, largely irreversible impact on cognitive development. Although it is almost impossible to discern the possible residual confounding in any observational study, several other prospective studies have also reported an inverse association between an early measure of lead exposure and subsequent developmental measures made in later childhood or early adulthood. Moreover, a number of animal studies have reported lasting effects of low-level lead exposure to lead in early life.

An alternative approach for testing the persistence of the effects of exposure to lead is to assess whether individual patterns of change in lead exposure are associated with individual changes in cognition. Ruff and colleagues found an association between decreases in blood lead levels and cognitive improvements in "moderately lead-poisoned" children after intervention, although the results of their study have been criticized for possible problems of residual confounding by age and educational factors.

No statistically significant association between declining blood lead levels and cognitive changes was observed in our data. However, there are several issues that need to be considered in interpreting our findings. First, blood lead levels may not be the best indicator of changes in exposure to lead. It is well known that blood lead is largely determined by variations in the magnitude and direction of recent exposure and may reflect only exposure that occurred recently (eg, within about 1 month).

Table 2.—Changes in Blood Lead Concentration and Children’s IQ Between Ages 7 and 11 to 13 Years

<table>
<thead>
<tr>
<th>Change in IQ Points*</th>
<th>Mean (SD)</th>
<th>95% Confidence Interval</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decline in Blood Lead Concentration, µmol/L (µg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.11 (&lt;2.3)</td>
<td>(n = 109)</td>
<td>−5.4 (8.3) -3.8 to −7.0</td>
<td></td>
</tr>
<tr>
<td>0.11-0.24 (2.3-4.9)</td>
<td>(n = 108)</td>
<td>−5.0 (9.3) -3.2 to −6.8</td>
<td>.45</td>
</tr>
<tr>
<td>&gt;0.24 (&gt;4.9)</td>
<td>(n = 109)</td>
<td>−3.8 (7.9) -2.3 to −5.3</td>
<td></td>
</tr>
</tbody>
</table>

*Change in IQ points between the ages of 7 and 11 to 13 years. †P value was calculated using the analysis of variance test.

Table 3.—Changes in Blood Lead Concentration and Cognitive Functioning Between Ages 2 and 4 and 11 to 13 Years

<table>
<thead>
<tr>
<th>Change in z Score*</th>
<th>Mean (SD)</th>
<th>95% Confidence Interval</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decline in Blood Lead Concentration, µmol/L (µg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between ages 2 and 11-13 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.49 (&lt;10.2) (n = 109)</td>
<td>0.03 (0.94)</td>
<td>−0.15 to 0.21</td>
<td></td>
</tr>
<tr>
<td>0.49-0.78 (10.2-16.2) (n = 108)</td>
<td>0.04 (1.01)</td>
<td>−0.15 to 0.23</td>
<td>.74</td>
</tr>
<tr>
<td>&gt;0.78 (&gt;16.2) (n = 109)</td>
<td>−0.01 (1.02)</td>
<td>−0.20 to 0.18</td>
<td></td>
</tr>
<tr>
<td>Between ages 4 and 11-13 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.29 (&lt;6.0) (n = 109)</td>
<td>0.05 (0.90)</td>
<td>−0.12 to 0.23</td>
<td></td>
</tr>
<tr>
<td>0.29-0.50 (6.0-10.3) (n = 108)</td>
<td>0.01 (0.91)</td>
<td>−0.17 to 0.18</td>
<td>.42</td>
</tr>
<tr>
<td>&gt;0.50 (&gt;10.3) (n = 109)</td>
<td>0.01 (0.96)</td>
<td>−0.17 to 0.19</td>
<td></td>
</tr>
</tbody>
</table>

*Change in z score between the ages of 2 and 11 to 13 years or 4 and 11 to 13 years. †P values were calculated using the analysis of variance test.

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References


