Blood Lead Levels and Serum Insulin-Like Growth Factor 1 Concentrations in Peripubertal Boys

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BACKGROUND: Childhood lead exposure has been associated with growth delay. However, the association between blood lead levels (BLLs) and insulin-like growth factor 1 (IGF-1) has not been characterized in a large cohort with low-level lead exposure.

METHODS: We recruited 394 boys 8–9 years of age from an industrial Russian town in 2003–2005 and followed them annually thereafter. We used linear regression models to estimate the association of baseline BLLs with serum IGF-1 concentration at two follow-up visits (ages 10–11 and 12–13 years), adjusting for demographic and socioeconomic covariates.

RESULTS: At study entry, median BLL was 3 μg/dL (range, <0.5–31 μg/dL); most boys (86%) were prepubertal, and mean ± SD height and BMI z-scores were 0.14 ± 1.0 and −0.2 ± 1.3, respectively. After adjustment for covariates, the mean follow-up IGF-1 concentration was 29.2 ng/mL lower (95% CI: −43.8, −14.5) for boys with high versus low BLL (≥5 μg/dL); this difference persisted after further adjustment for pubertal status. The association of BLL with IGF-1 was stronger for mid-pubertal than prepubertal boys (p = 0.04). Relative to boys with BLL < 2 μg/dL, adjusted mean IGF-1 concentrations decreased by 12.8 ng/mL (95% CI: −29.9, 4.4) for boys with BLLs of 3–4 μg/dL; 34.5 ng/mL (95% CI: −53.1, −16.0) for BLLs 5–9 μg/dL; and 60.4 ng/mL (95% CI: −90.9, −29.9) for BLLs ≥ 10 μg/dL.

CONCLUSIONS: In peripubertal boys with low-level lead exposure, higher BLLs were associated with lower serum IGF-1. Inhibition of the hypothalamic–pituitary–growth axis may be one possible pathway by which lead exposure leads to growth delay.

KEY WORDS: cohort studies, growth, insulin-like growth factor 1, lead, puberty.

Blood lead level and serum IGF-1 concentration

Venous blood samples were collected in trace metal-free Vacutainer tubes (Becton-Dickinson, Franklin Lakes, NJ, USA), after cleansing the venipuncture site with alcohol. Whole-blood samples were diluted with a matrix modifier solution (WHO 2011). For this analysis, the World Health Organization (WHO) recommendation for BLLs categorized as high (> 5 μg/dL) versus low (≤ 5 μg/dL) was followed. The intra-assay coefficient of variation (CV) was < 3.9%, and the inter-assay CV was < 8.1% for the Immulite 2000 kit.

Statistical analysis. We used repeated measures analysis to estimate the association between BLL measured at 8–9 years of age and serum IGF-1 concentration at both the 2-year (at 10–11 years) and 4-year (at 12–13 years) follow-up visits. The distribution of BLLs was right-skewed with outliers. We considered several different ways of evaluating BLLs, including dichotomized as high (≥ 5 μg/dL) versus low (< 5 μg/dL) based on the new CDC threshold, as a continuous measure (log-transformed), and categorized as 0–2, 2–3, 3–4, 4–5, 5–9, or ≥ 10 μg/dL.

We fit linear regression models using a generalized estimating equation (GEE) approach to account for the repeated measures and slight skewness of IGF-1 concentrations. We first fit GEE linear regression models to evaluate unadjusted associations of high versus low BLL (≥ 5 or < 5 μg/dL) with serum IGF-1 concentrations. Next, we created a full multivariable model that included dichotomized BLL, birth weight (continuous), gestational age at birth (continuous), breastfeeding duration (< 12, 12–24, or > 24 weeks), maximum parental education (secondary education or less, junior college/technical training, or university graduate), monthly household income (< US$175, $175–250, or > $250), nutritional intake (total caloric intake and percent calories from protein, fat, and carbohydrate as continuous variables), baseline and follow-up age (continuous), and baseline and follow-up BMI [underweight (BMI < 10th percentile), overweight (BMI > 85th percentile), or normal weight]. We decided a priori not to consider height as a covariate due to its strong correlation with IGF-1 during puberty (Silbergeld et al. 1986). We then reduced this model by excluding covariates that did not predict the outcome with p ≤ 0.10, or did not change the estimated association between BLL and IGF-1 by > 10% when removed from the model, resulting in a final model that included baseline parental education, birth weight, nutritional intake, and baseline and follow-up age and BMI.

Results

Baseline growth and demographic characteristics of the 394 boys included are shown in Table 1. The 95 eligible boys excluded from the present analysis were not significantly different from those included with regard to the characteristics shown in Table 1, except that they tended to have a higher percent protein intake at baseline and were more likely to have parents that had junior college or technical training (data not shown).

The median BLL at 8–9 years of age among boys included in the analysis was 3 μg/dL (25th, 75th percentiles: 2 μg/dL, 5 μg/dL; range, 0.5–31 μg/dL). Most boys were prepubertal at baseline. The mean baseline height z-score was slightly above the WHO average, and the mean baseline BMI z-score was slightly below the WHO average (Table 1).

In unadjusted GEE models that accounted only for correlation among study visits, mean serum IGF-1 concentration during follow-up was 24.3 ng/mL lower (95% CI: −39.3, −9.3) among boys with BLL ≥ 5 μg/dL compared with those with < 5 μg/dL. A significantly lower mean IGF-1 concentration for boys with high versus low BLL was also estimated based on the full multivariable model (−28.0 ng/mL; 95% CI: −43.1, −12.9) and the final reduced model (−29.2 ng/mL; 95% CI: −43.8, −14.5).
Table 1. Baseline and follow-up characteristics of 394 boys from Chapaevsk, Russia, with baseline blood lead levels and two longitudinal measures of serum IGF-1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>8–9 years old (baseline)</th>
<th>10–11 years old</th>
<th>12–13 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (median (range))</td>
<td>8.1 (7.8–9.4)</td>
<td>10.1 (9.9–11.5)</td>
<td>12.1 (11.9–13.5)</td>
</tr>
<tr>
<td>BMI (WHO z-score)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>–0.2 ± 1.3</td>
<td>–0.2 ± 1.3</td>
<td>–0.2 ± 1.4</td>
</tr>
<tr>
<td>≤ 10th percentile (%[n(%)])</td>
<td>67 (17)</td>
<td>83 (21)</td>
<td>75 (19)</td>
</tr>
<tr>
<td>&gt; 85th percentile (%[n(%)])</td>
<td>58 (15)</td>
<td>83 (21)</td>
<td>70 (18)</td>
</tr>
<tr>
<td>Height (WHO z-score) (mean ± SD)</td>
<td>0.14 ± 1.0</td>
<td>0.14 ± 1.0</td>
<td>0.03 ± 1.1</td>
</tr>
<tr>
<td>Testicular volume (ml) [median (IQR)]</td>
<td>235 ± 115.9</td>
<td>235 ± 115.9</td>
<td>235 ± 115.9</td>
</tr>
<tr>
<td>IQR, interquartile range.</td>
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</tr>
</tbody>
</table>

Table 2. Repeated measures generalized estimating equation models predicting the mean levels of serum concentrations of IGF-1 (ng/mL) in relation to blood lead levels and relevant covariates.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Full multivariable model (n = 385 boys, 767 visits)</th>
<th>Final reduced model (n = 389 boys, 775 visits)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted mean change (95% CI) p-Value</td>
<td>Adjusted mean change (95% CI) p-Value</td>
</tr>
<tr>
<td>Lead (µg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>≥ 5</td>
<td>–28.0 (–43.1, –12.9) &lt; 0.001</td>
<td>–29.2 (–43.8, –14.5) &lt; 0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51.9 (47.2, 56.8) &lt; 0.001</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 175</td>
<td>–17.4 (–32.5, –1.5) 0.03</td>
<td>–18.6 (–34.2, –2.9) 0.03</td>
</tr>
<tr>
<td>&gt; 175</td>
<td></td>
<td></td>
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<tr>
<td>Nutritional intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total calories [kcal/day]</td>
<td>–2.6 (–10.7, 6.5) 0.54</td>
<td>–2.6 (–10.6, 5.5) 0.54</td>
</tr>
<tr>
<td>Fat (percent)</td>
<td>1.4 (0.2, 2.6) 0.02</td>
<td>1.3 (0.1–2.5) 0.03</td>
</tr>
<tr>
<td>Protein (percent)</td>
<td>3.0 (–1.6, 7.6) 0.21</td>
<td>3.1 (–1.4, 7.6) 0.18</td>
</tr>
<tr>
<td>Parental education</td>
<td></td>
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<tr>
<td>Secondary education or less</td>
<td>–22.5 (–45.8, 0.8) 0.06</td>
<td>–24.9 (–47.7, –2.0) 0.03</td>
</tr>
<tr>
<td>Junior college/technical training</td>
<td>–3.4 (–19.3, 12.5) 0.69</td>
<td>–2.7 (–18.4, 13.0) 0.74</td>
</tr>
<tr>
<td>University graduate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly household income (US$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 175</td>
<td>–3.3 (–20.3, 13.8) 0.71</td>
<td>–3.3 (–20.3, 13.8) 0.71</td>
</tr>
<tr>
<td>&gt; 175</td>
<td>–6.4 (–32.7, 10.9) 0.47</td>
<td>–3.8 (–32.7, 10.9) 0.47</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 24</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt; 24</td>
<td>0.7 (–18.2, 19.7) 0.94</td>
<td>1.1 (–14.1, 16.4) 0.88</td>
</tr>
</tbody>
</table>

Figure 1. Adjusted mean IGF-1 concentrations for high versus low BLL by pubertal status. The adjusted mean IGF-1 difference for high versus low BLL was 14 ng/mL in prepubertal boys, 18 ng/mL in early-pubertal boys, and 42 ng/mL in mid-pubertal boys. Compared with prepubertal boys, the lead-associated IGF-1 difference was larger in mid-pubertal boys (p = 0.04) and larger, but not significantly larger, in early-pubertal boys (p = 0.65).
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Concentrations (Afeiche et al. 2012). Also, none of the participants had a baseline IGF-1 measurement. However, we believe that a prospective evaluation of BLL on subsequent IGF-1 values made for a stronger study design.

Future studies of lead and growth would benefit from measurement of serum insulin-like growth factor-binding protein 3, a less nutritionally dependent measure of GH activity. Inclusion of girls in future studies will also be important, because rodent models suggest that lead’s effect on pubertal growth may be more pronounced in males than in females (Ronis et al. 1998a). Furthermore, the net effect of lead on growth in humans cannot be completely understood without information on the association between childhood lead exposures and adult height, so continued longitudinal follow-up through adulthood is warranted for this and other cohorts.

Conclusion

In the present study we found a negative monotonic dose–response association between blood lead levels in boys at 8–9 years of age and their serum IGF-1 concentrations at 10–11 and 12–13 years of age. With increasing attention to environmental exposures and potential health risks, it is essential to better understand effects of low-level lead exposure on key developmental processes such as growth and reproductive development.

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