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Accessibility
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 versus low BLL (≥ 5 μg/dL or < 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 BLLs < 2 μg/dL, adjusted mean IGF-1 concentrations decreased by 12.8 ng/mL (95% CI: −32.9, 4.4) for boys with BLLs of 3–4 μg/dL; 43.4 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 prepubertal 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.

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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.

| Variable                                    | 8–9 years old (baseline) | 10–11 years old | 12–13 years old |
|---------------------------------------------|--------------------------|-----------------|-----------------|
| Age (years) [median (range)]                | 8.1 (7.8–9.4)            | 10.1 (9.9–11.5) | 12.1 (11.9–13.5) |
| BMI (WHO z-score)                           |                          |                 |                 |
| Mean ± SD                                   | –0.2 ± 1.3               | –0.2 ± 1.3      | –0.2 ± 1.4      |
| ≤ 10th percentile [n (%)]                   | 67 (17)                  | 83 (21)         | 75 (19)         |
| > 95th percentile [n (%)]                   | 58 (15)                  | 83 (21)         | 70 (18)         |
| Height (WHO z-score) [mean ± SD]            | 0.14 ± 1.0               | 0.14 ± 1.0      | 0.03 ± 1.1      |
| Testicular volume [mL] [n (%)]              |                          |                 |                 |
| ≤ 3 (prepubertal)                           | 336 (68)                 | 213 (54)        | 52 (13)         |
| > 3–6                                       | 55 (14)                  | 153 (39)        | 104 (27)        |
| > 6                                         | 0 (0)                    | 28 (7)          | 235 (60)        |
| IGF-1 (ng/mL) [mean ± SD]                   |                          |                 |                 |
| Birth weight [kg] [mean ± SD]               | 3.34 ± 0.52              | 146.9 ± 52.1    | 253.5 ± 115.9   |
| Breastfeeding duration (weeks) [median (IQR)] | 13.0 (30.3)             |                 |                 |
| Baseline nutritional intake (mean ± SD)     |                          |                 |                 |
| Total kcal/day                              | 2,837 ± 972              |                 |                 |
| Percent fat                                 | 34.1 ± 5.8               |                 |                 |
| Percent protein                             | 11.5 ± 1.6               |                 |                 |
| Percent carbohydrate                        | 54.5 ± 6.5               |                 |                 |
| Monthly household income (US$) [n (%)]      |                          |                 |                 |
| < 175                                       | 136 (35)                 |                 |                 |
| > 175                                       | 175–250                  | 107 (27)        |                 |
| > 250                                       | 150 (38)                 |                 |                 |
| Maximal parental education [n (%)]          |                          |                 |                 |
| Secondary education or less                 | 25 (6)                   |                 |                 |
| University graduate                         | 244 (62)                 |                 |                 |
| Blood lead level (μg/dL)                    |                          |                 |                 |
| Median (IQR)                                | 3.0 (3.0)                |                 |                 |
| < 5 [n (%)]                                 | 285 (72)                 |                 |                 |
| ≥ 5 [n (%)]                                 | 109 (28)                 |                 |                 |

IQR, interquartile range.

*Five subjects missing. †Two subjects missing. ‡Five subjects missing. §One subject missing.

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.

| Covariate | Full multivariable model (n = 385 boys, 767 visits) | Final reduced model (n = 389 boys, 775 visits) |
|-----------|-----------------------------------------------------|-----------------------------------------------|
|           | Adjusted mean change (95% CI) p-Value               | Adjusted mean change (95% CI) p-Value         |
| Lead (μg/dL) | Reference                                              | Reference                                      |
| < 5        | −28.0 (−43.1, −12.9)                                  | −29.2 (−43.8, −14.5)                          | < 0.001 |
| ≥ 5        | 51.9 (47.2, 56.6)                                    | 52.1 (42.4, 56.8)                             | < 0.001 |
| Age (years) | Reference                                              | Reference                                      |
| ≤ 10       | −17.4 (−32.2, −1.5)                                  | −17.5 (−31.5, −3.5)                           | 0.01    |
| > 10–15    | 13.8 (−4.4, 31.9)                                    | 12.9 (−5.2, 30.9)                             | 0.16    |
| Nutritional intake | Reference                                              | Reference                                      |
| Total calories | −2.6 (−10.7, 5.6)                                    | −2.6 (−10.6, 5.5)                             | 0.54    |
| Fat (percent) | 1.4 (0.2, 2.6)                                        | 1.3 (0.1–2.5)                                 | 0.03    |
| Protein (percent) | 3.0 (−1.6, 7.6)                                      | 3.1 (−1.4, 7.6)                               | 0.18    |
| Parental education | Reference                                              | Reference                                      |
| Secondary education or less | −22.5 (−45.8, 0.8)                                  | −24.9 (−47.7, −2.0)                           | 0.03    |
| Junior college/technical training | −3.4 (−19.3, 12.5)                                  | −2.7 (−18.4, 13.0)                            | 0.74    |
| University graduate | Reference                                              | Reference                                      |
| Monthly household income (US$) | Reference                                              | Reference                                      |
| < 175      | −3.3 (−3.1, 3.8)                                     | 0.71                                          |
| > 125      | −3.4 (−3.3, 3.0)                                     | 0.47                                          |
| Gestational age (weeks) | Reference                                              | Reference                                      |
| < 24       | 0.7 (−18.2, 19.7)                                    | 0.94                                          |
| ≥ 24       | 1.1 (14.1, 16.4)                                     | 0.88                                          |

Table 2. When pubertal status was added to the final reduced model, the association of high BLL with IGF-1 concentration was modestly attenuated (adjusted mean difference = −24.4 ng/mL; 95% CI: −37.7, −11.1).

The association of BLL with IGF-1 concentration differed according to pubertal status. In particular, the reduction in adjusted mean IGF-1 concentrations between high versus low BLL groups was greater among boys in mid-puberty than for prepubertal boys (−41.9 ng/mL; 95% CI: −15.1, −68.7 vs. −14.1 ng/mL; 95% CI: −0.9, −27.2; interaction p-value = 0.04). The reduction in adjusted mean IGF-1 concentrations between high versus low BLL groups was slightly larger for boys in early puberty (−18.0 ng/mL; 95% CI: −3.5, −32.5) than for prepubertal boys (interaction p-value = 0.64) (Figure 1). Adjusted mean percent decrease in IGF-1 concentrations between high versus low BLL groups were 9.3%, 12.2%, and 19.5% for prepubertal boys, boys in early puberty, and boys in mid-puberty, respectively.

In sensitivity analyses, further adjustment for parental heights among the subset of boys (n = 337) with these measures available had no appreciable impact on the estimated difference in IGF-1 concentrations for boys with high versus low BLL (adjusted mean difference = −31.6 ng/mL; 95% CI: −48.2, −15.0).

The estimated difference in IGF-1 was also similar based on a model that included follow-up IGF-1 concentrations for 438 boys with at least one IGF-1 measurement (adjusted mean difference = −28.8 ng/mL; 95% CI: −42.5, −15.1).

When BLL was divided into finer categories, adjusted mean IGF-1 concentrations decreased monotonically relative to high BLL (Table 2).
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Discussion

We observed a negative association between BLLs measured at 8–9 years of age and serum IGF-1 concentrations at 10–11 and 12–13 years of age that was stronger among boys in mid-puberty than in prepubertal boys. This finding suggests one possible explanation for our previous finding of lower mean height z-scores for boys in the same cohort with BLL ≥ 5 μg/dL compared with BLL < 5 μg/dL (Burns et al. 2012). Results from the present analysis suggest a monotonic dose–response relationship between BLL and serum IGF-1 that adds further support to existing evidence of physiological effects of BLLs < 10 μg/dL (Ballew et al. 1999; Bellinger et al. 1992; Gump et al. 2005; Kafourou et al. 1997; Karmaus et al. 2005; Lanphear et al. 2005; Little et al. 2009; Menke et al. 2006; Naicker et al. 2010; Selevan et al. 2003; Shukla et al. 1991; Williams et al. 2010).

A negative association between BLL and serum IGF-1 concentrations is consistent with lead-induced inhibition of the hypothalamic–pituitary–growth axis. An in vitro study in rat pituitary demonstrated that lead blocked the binding of growth hormone releasing hormone to its receptor, suggesting axis inhibition at the level of the pituitary (Lau et al. 1991). Lead could also affect the growth axis at the level of the pituitary through interference with calcium-dependent GH release. In in vitro studies of bovine and rat pituitary, other divalent cations such as zinc, nickel, cadmium, and magnesium blocked calcium-dependent GH release (Carlson 1984; Lorenson et al. 1983), although additional studies are needed to determine whether this effect persists in vivo and whether lead elicits similar actions. Consistent with these potential pituitary-mediated effects, a study of rodent pups (mean BLL, 18 μg/dL) demonstrated suppressed growth hormone releasing hormone-stimulated GH release (Camoratto et al. 1993), and in a separate rodent model, high lead exposure (up to mean BLL of 263 μg/dL) resulted in lower serum IGF-1 concentrations and lower serum IGF-1 concentrations before chelation (BLLs > 40 μg/dL) compared with after chelation (BLLs ≤ 30 μg/dL) (Huseman et al. 1992). In contrast to these studies, the present analysis explored BLLs within currently acceptable ranges and still found a negative association between BLL and IGF-1.

Lead may also inhibit the reproductive axis at the level of the pituitary. Six men with occupational lead exposure (mean BLL, 30.7 μg/dL) had blunted LH response to gonadotropin-releasing hormone (GnRH) compared with nine men without occupational exposure (mean BLL, 16 μg/dL) (Bronstein et al. 1978). In a study of 77 lead smelter workers (mean BLL, 33 μg/dL) and 26 nonworkers (mean BLL, 4.1 μg/dL), a subset analysis demonstrated lowered GnRH-stimulated follicle-stimulating hormone in 9 workers compared to 11 nonworkers (Erfurth et al. 2001). Also, lead exposure in rodents resulted in decreased serum LH concentrations (Ronis et al. 1998b) and increased pituitary LH stores (Klein et al. 1994; Sokol et al. 1998), further suggesting possible pituitary hyporesponsiveness to GnRH. Consistent with these studies of gonadotropin inhibition, lead exposure has been associated with later onset of puberty in our cohort (Williams et al. 2010) and in other adolescent cohorts (Naicker et al. 2010; Selevan et al. 2003).

A lead-induced decrement in IGF-1 may contribute to gonadotropin inhibition and pubertal delay. Specifically, IGF-1 has been shown to activate GnRH in vitro (Zhen et al. 1997) and in rodent models (Hiney et al. 1991, 1996), and puberty is delayed in GnRH-specific IGF-1 receptor knockout mice (Divall et al. 2010). Furthermore, IGF-1 administration to lead-exposed mice with delayed puberty restored pubertal timing (Pine et al. 2006), providing additional evidence for a potential mediating role of IGF-1 in the association between lead exposure and delayed puberty.

In addition to inhibition of GH and gonadotropin release, in animal studies, high lead exposure has been associated with other processes that could lead to growth delay such as decreased food consumption (Hammond et al. 1989, 1990) and reduced formation of new bone (Hass et al. 1967; Hicks et al. 1996). Future studies should explore whether these effects can be observed in humans with low-level lead exposures.

As far as we are aware, our study is the first to identify puberty as a particularly vulnerable period in which to assess lead’s effect on IGF-1. Both the absolute and percent decrease in IGF-1 in association with lead exposure was larger in mid-pubertal boys than in prepubertal or early-pubertal boys. Thus, in our cohort, puberty seemed to be a key time period in which to detect an effect of lead, and this may be generalizable to other environmental epidemiologic studies examining outcomes of growth and associated hormones.

The present study is limited by availability of the BLL measurement at only one time point, leading to an inability to explore other vulnerable windows of exposure, such as exposures during infancy that may have a stronger association with childhood height (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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