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Peripubertal blood lead levels and growth among Russian boys

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ABSTRACT

Background: Childhood blood lead levels (BLL) have been associated with growth impairment.
Objectives: We assessed associations of peripubertal BLL with adolescent growth and near adult height in a longitudinal cohort of Russian boys.
Methods: 481 boys were enrolled at ages 8–9 years and followed annually to age 18. At enrollment, BLL was measured, and height, weight, and pubertal staging were obtained annually during 10 years of follow-up. Mixed effects models were used to assess the associations of BLL with longitudinal age-adjusted World Health Organization *Z*-scores for height (HT-*Z*) and body mass index (BMI-*Z*), and annual height velocity (HV). Interactions between boys' age and BLL on growth outcomes were evaluated.
Results: The median (range) BLL was 3.0 (0.5–31.0) μg/dL. At age 18 years, 79% of boys had achieved near adult height (HV < 1.0 cm/year), and means (SD) for HT-*Z* and BMI-*Z* were 0.15 (0.92) and − 0.32 (1.24). Over 10 years of follow-up, after covariate adjustment, boys with higher (≥ 5 μg/dL) BLL compared with lower BLL were shorter (adjusted mean difference in HT-*Z* = − 0.43, 95% CI − 0.60, − 0.25, *p*-value < 0.001), translating to a 2.5 cm lower height at age 18 years. The decrement in height for boys with higher BLL was most pronounced at 12 to 15 years of age (interaction $p = 0.03$). Boys with higher BLL were leaner (adjusted mean difference in BMI-*Z* = − 0.22, 95% CI: − 0.45, 0.01, $p = 0.06$).
Conclusions: Higher peripubertal BLLs were associated with shorter height through age 18 years, suggesting a persistent effect of lead on linear growth.

1. Introduction

Exposure to lead during childhood has been associated with a broad spectrum of deleterious health effects (Bellinger, 2011). Although childhood lead exposure in the U.S. has been dramatically reduced over the past 50 years, primarily through elimination of leaded gasoline and paint and lead abatement in housing stock, blood lead levels (BLLs) above the CDC's current reference level of 5 μg/dL continue to be seen, particularly in lower socio-economic communities (Raymond and Brown, 2015) and areas contaminated from industrial sources (Brink et al., 2016; Laidlaw et al., 2016). There is renewed interest in the effects of lead on children's health in the U.S due to recent incidents of increased lead exposure via contaminated drinking water from lead-containing water distribution and plumbing infrastructure (Hanna-Attisha et al., 2016).

High BLL in childhood has been associated with neurological and behavioral effects (Rauh and Margolis, 2016) and later pubertal onset (Hauser et al. 2009; Selevan et al., 2003; Williams et al., 2010; Wu

Abbreviations: BLL, blood lead level; BMI-*Z*, body mass index z-score; CI, confidence interval; HT-*Z*, height z-score; HV, height velocity; SD, standard deviation; SES, socio-economic status; WHO, World Health Organization

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et al., 2003). Evidence also links high BLL during early childhood with lower height and weight (Ballew et al., 1999; Cantoral et al., 2015; Cassidy-Bushrow et al., 2016; Ignasiak et al., 2006; Kafourou et al., 1997; Little et al., 2009; Min et al., 2008; Schwartz et al., 1986). However, no longitudinal studies have examined whether the negative effects of lead on height and body mass index (BMI; kg/m^2) in childhood persist and ultimately result in reduced adult height.

Previously, we reported that higher peripubertal BLLs (≥ 5 μg/dL) measured at age 8 to 9 years in our cohort were associated with lower height (Burns et al., 2012), delayed pubertal onset (Hauser et al. 2009; Williams et al., 2010) and reduced insulin-like growth factor 1 (IGF-1) (Fleisch et al., 2013) at ages 12–13 years. In the current analysis, we assess the longitudinal relationship of peripubertal BLL with height and BMI over 10 years of follow-up, through age 18, when most young men have achieved sexual maturity (Burns et al., 2016) and adult height.

2. Methods

2.1. Study population

The Russian Children's Study is a prospective cohort of 499 boys residing in Chapaevsk, Russia, enrolled in 2003–2005 at ages 8–9 years (Hauser et al., 2005) and followed annually through 2012–2015 to age 18 years. For this analysis, 10 boys in the original cohort were excluded due to chronic illnesses that could affect growth and/or pubertal development. Of the remaining 489 subjects, 481 (98%) with baseline BLL measurements were included for this analysis. The study was approved by the Human Studies Institutional Review Boards of the Chapaevsk Medical Association, Harvard T.H. Chan School of Public Health, University of Massachusetts Medical School, and Brigham and Women's Hospital. Before participation, the parent/guardian provided informed consent and the boys signed assent forms; at age 18 years the young men signed informed consent forms.

At study entry, each boy's parent or guardian completed nurse-administered health and lifestyle questionnaires (Lee et al., 2003), ascertaining birth and medical history, and demographic and socioeconomic status (SES) information. A validated Russian Institute of Nutrition semi-quantitative food frequency questionnaire was used to characterize each child's diet (Martinchik et al., 1998; Rockett et al., 1997).

2.2. Physical examination

At study entry and annual follow-up visits, a standardized anthropometric examination (http://www.cdc.gov/nchs/products/elec_prods/subject/video.htm) was performed by a trained research nurse and pubertal staging was performed by a single physician-investigator (O.S.) according to a written protocol. Height was measured to the nearest 0.1 cm using a stadiometer. Weight was measured to the nearest 100 g with a metric scale. Age-adjusted z-scores were calculated for height (HT-*Z*) and BMI (BMI-*Z*) using the World Health Organization standards (WHO) (World Health Organization 2007). Annual height velocity (HV) was calculated by computing the difference in height between visits adjusted to one year increments (cm/year).

2.3. Blood sample analysis for lead measurement

At study entry, a 3.0-mL venous blood sample was collected in a trace metal-free vacutainer tube (Becton-Dickinson, Franklin Lakes, NJ) after alcohol cleansing of the skin. Whole-blood samples were diluted with a matrix modifier solution and analyzed for lead by Zeeman background-corrected, flameless graphite furnace, atomic absorption spectrometry (ESA Laboratories, Chelmsford, MA). The detection limit was 1.0 μg/dL; 14 (2.9%) of the 481 boys had BLLs below the limit of detection.

2.4. Statistical analysis

We used mixed effects linear regression models to evaluate the associations of high BLL (≥ 5 versus < 5 μg/dL) at age 8–9 years with age-adjusted BMI-*Z*, HT-*Z*, and annual HV measured over ten years of follow-up (through age 18 years). An autoregressive covariance structure was utilized to account for within-boy correlation in growth measures over time. Initially we evaluated unadjusted associations of higher versus lower BLL with each growth outcome. We then fit a full multivariable model including all covariates with univariate $p \leq 0.20$; these included maternal prenatal exposure to tobacco smoke (either active or passive), birth weight, gestational age, breastfeeding duration, and covariates at baseline including boys' nutritional intake (total caloric intake and proportions of calories from protein, fat, and carbohydrates) and beer consumption, parental education, household income, residence of biological father in the home, number of siblings, and age. Final models for each outcome were reduced, retaining covariates with $p < 0.10$ in the multivariable analysis, or which changed the high BLL effect estimate by > 10%. The final models for both HT-*Z* and BMI-*Z* included age and birth weight; in addition, the model for HT-*Z* included preterm vs. term birth and percent calories from protein whereas the model for BMI-*Z* included no biological father in the home and percent calories from fat. We also evaluated associations of growth outcomes with $\log_e$-transformed BLL. We evaluated interactions between age (closest integer year) and high BLL (≥ 5 μg/dL) for each outcome using an overall Wald chi-square test for cross-product terms (10df for HT-Z and BMI-Z, 9df for HV). In sensitivity analyses conducted to assess the dose-response relationship at lower BLLs, we restricted the data to BLL ≤ 5 μg/dL and evaluated the associations of categories of BLL (≤ 2, 3, 4, and 5 μg/dL) with growth. Parameter estimates were obtained using restricted maximum likelihood methods implemented via PROC MIXED in SAS Version 9.4 (SAS Institute, Cary NC). We defined near final adult height as the first height at which HV was < 1 cm/yr. The mean age and near adult height were estimated using PROC LIFEREG with right censoring for boys who had not yet attained adult height. Statistical significance was defined as two-sided *p*-values ≤ 0.05.

3. Results

3.1. Study population

Table 1 summarizes perinatal history and baseline characteristics overall and by BLL; anthropometric measurements at entry and age 18 are also provided.

Among the 481 boys, the median (interquartile range) of BLL was 3.0 (2.0–5.0) μg/dL; the distribution was right skewed, 10 (2.1%) boys had BLL ≥ 10 μg/dL at entry (Hauser et al., 2009). On average, boys with BLL > 5 μg/dL had lower birthweight, breastfed longer, more often had mothers who drank alcohol and smoked tobacco during pregnancy, were from households with lower socioeconomic status (SES), and were significantly shorter. At study entry, 14% of boys had signs of pubertal onset. Of the original cohort, 305 (61%) boys completed follow-up through age 18 years; those remaining in the study were more often full term at birth (94% vs 87%), with younger mothers (23.5 vs. 24.6 years), and a higher percentage of parents with post-secondary education (95% vs. 87%) than those who discontinued. There were no substantial differences for other anthropometric or demographic characteristics.

3.2. Growth measures at entry and during follow-up

Most boys were within the normal range for height and BMI both at entry and at age 18 (Table 1) (de Onis et al., 2007). Annual HV was greatest at 14 years (mean HV (SD) = 7.5 (2.3) cm/yr). By age 18 years, 79% had achieved near adult height. The overall mean height