GROWTH AND MATURATION IN HUMAN BIOLOGY AND SPORTS

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EDITORS

IMPACT OF ELEVATED BLOOD LEAD ON GROWTH, MATURATION AND PHYSICAL FITNESS: RESEARCH IN THE COPPER BASIN OF SOUTHWESTERN POLAND

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INTRODUCTION:
Lead and Child Growth, Development, and Maturation

Environmental pollutants and toxicants associated with industry and power generation and have potentially negative consequences for the growth, maturation and development of youth. Lead is one of a variety of toxicants with such potential effects. Lead and lead compounds are common in the earth's crust, ~70 ppm (Baselt, 2002) and are associated with power generation and several industrial processes. Lead and lead-compounds are well-known to be toxic to developing humans, causing growth retardation, delayed sexual maturation and neurobehavioral developmental deficits.

  <u>Lead and Growth.</u> Elevated levels of blood lead adversely affect prenatal growth (Andrews et al., 1994; Dietrich et al., 1987), but this has not been noted in all studies (McMichael et al., 1986; Factor-Litvak et al., 1991). A frequent finding among children is reduced length/stature in association with increased blood lead levels. Age at exposure, duration, and nutritional status are related to the degree of growth stunting, with younger, chronically exposed, undernourished children at greatest risk (Ballew et al., 1999). The estimated stunting effect of blood lead level on linear growth appears to follow a dose-related pattern of reduction in height by ~1-3 cm for each 10.0 µg/dL increase in blood lead level (Table 1).

  <u>Lead and Maturation.</u> Information on the influence of elevated blood lead levels on indicators of biological maturation commonly used in growth studies is limited largely to age at menarche and to a lesser extent stages of puberty (breast and pubic hair development in girls, genital and pubic hair development in boys).

Table 1. Estimated decrements in height per 10 μg/dL blood lead levels in children 3 months (mos) to 14 years (yrs).

Study	Age range	Stature decrement
Cincinnati Lead Study (Shukla et al., 1989)	3 - 5 mos	2.0 cm
Cincinnati Lead Study (Shukla et al., 1991)	33 mos	1.5 cm
Dallas Lead Project I (Little et al., 1990)	1 - 10 yrs	1.6 cm
Dallas Lead Project II (Little et al., 2009)	2 - 12 yrs	2.1 cm
Three Greek Cities (Kafourou et al., 1997)	6 - 9 yrs	0.9 cm
NHANES II (Schwartz et al., 1986)	1 - 7 yrs	1.2 cm
NHANES III (Ballew et al., 1999)	1 - 7 yrs	1.6 cm
Lower Silesia, Poland (Ignasiak et al., 2006)	7 - 14 yrs	3.1 cm
Unweighted Mean	3 mos - 14 yrs	2.5 cm

Blood lead levels > 3 μg/dL were associated with later estimated attainment of stages of breast and pubic hair maturation in American girls from the Third National Health and Nutrition Examination Survey, 1988-1994 (NHANES III). Later attainment of stages of puberty was most apparent in American Black girls and to a lesser extent in Mexican American girls with ≤ 3.0 μg/dL of blood lead compared to those with >3.0 μg/dL. Later pubertal maturation was noted in American White girls with 3.0 μg/dL of blood lead, but the effect was not significant (Selevan et al., 2003). Corresponding data for lead levels and sexual maturation of boys are limited to a prospective study of testicular volume and stages of pubic hair and genital maturation in Russian boys. Later onset of puberty was associated with blood lead levels ≥5.0 μg/dL compared to boys with <5.0 μg/dL (Hauser et al., 2008; Williams et al., 2011).

Data for age at menarche and blood lead level are limited to three investigations. Two analyses were of the same national data set for American girls from NHANES III (Selevan et al., 2003; Wu et al., 2003), and one of American Indian girls (Denham et al., 2005). The two analyses of NHANES III data showed delayed menarche with elevated blood lead levels in American girls. In one analysis, menarche was delayed by approximately 3.6 months for each 1.0 μg/dL increase in blood lead > 3.0 μg/dL (Wu et al., 2003). In the other analysis, menarcheal age was also delayed by 3.6 months with blood lead concentrations > 3.0 μg/dL in African American girls. However, blood lead and later menarche was not statistically significant in American White and Mexican American girls with lead concentrations > 3.0 μg/dL (Selevan et al., 2003). Menarche was delayed at blood lead levels >0.5 μg/dL (geometric mean) among American Indian (Akwesasne Mohawk) girls (Denham et al., 2005). This study was unique because the analysis controlled for other pollutants (*p,p'*-DDE, HCB, mirex and mercury) in addition to lead. In contrast to lead, four potentially estrogenic PCB congeners were associated with a higher probability of having attained menarche in this sample of American Indian

girls (Denham et al., 2005), indicating earlier attainment of menarche with higher PCB levels. Importantly, the association of blood lead level with age at menarche is likely confounded by other toxicants in the blood.

Lead and Motor Proficiency. Elevated blood lead levels are associated with impaired performances on tests of fine motor coordination and visual integration in children. Specifically, movement tasks that involve movement precision and coordination are adversely affected by elevated blood lead levels. Among 6 year old children, for example, elevated blood lead levels had a negative effect visual-motor control, bilateral coordination, upper limb speed of movement, dexterity and fine motor coordination (Dietrich et al., 1993), and on finger tapping speed (Winneke et al., 1994). Visual-motor integration, eye-hand coordination and spatial relations performance was poorer among 8-10 year old children with increased blood lead levels (Azcuno-Cruz et al., 2000). Of interest, high lead levels in dentin of deciduous teeth (i.e., in early childhood) were also associated with long term deficits in finger tapping rate (slower), eye-hand coordination (poorer) and reaction time (slower) at 18 years of age (Needleman et al., 1990). Neurobehavioral deficits associated with elevated blood lead levels persist across age and are apparently irreversible.

With few exceptions, tasks requiring muscular strength and endurance, speed, power, balance and coordination in gross movement tasks have not been systematically evaluated in children and adolescents with elevated blood lead levels. Gross balance at 6 years of age (Dietrich et al., 1993) and performance on rail balance tests at 8-10 years of age (Azcuna-Cruz et al., 1970) were not influenced by blood lead levels. Elevated blood lead levels were negatively associated with teacher ratings of agility defined as ''…the ability to execute motor activities such as running and jumping with precision and rapidity,'' in 7-9 year old children (Muñoz et al., 1993). Increased postural sway in children was associated with elevated blood lead levels (Battacharya et al., 1990, 1993), but the association between postural sway and balance was not analyzed. If postural sway is analyzed with respect to dynamic and static balance, these results may suggest a potential influence of early lead exposure on the vestibular system and/or proprioception. Elevated blood lead was also associated with hearing deficits in children (Osman et al., 1999). Apparently lead affects middle ear function (i.e., otolithic and vestibular complexes).

THE COPPER BASIN – RECENT WORK ON LEAD EFFECTS ON CHILDREN BY MALINA AND COLLEAGUES

The copper mine region in Lower Silesia, southwestern Poland, has major smelting and refinery facilities near Legnica and Głogów, the Copper Basin (Figure 1). Mines and smelting plants associated with the copper industry generate large amounts of industrial by-products and waste including heavy metals, including lead. Copper mining and smelting has been a primary industrial activity for about two generations or more in Lower Silesia.
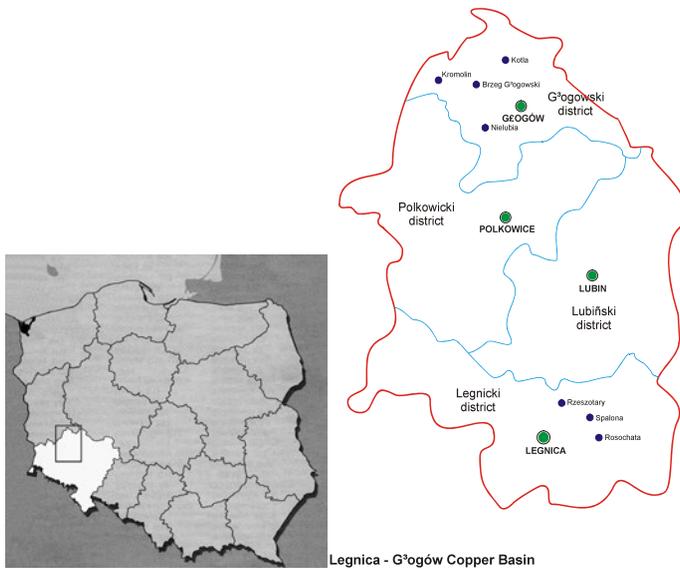
Figure 1. Map of Poland showing (a) the region and (b) the location of the study communities. (Adapted from Ignasiak et al., 2006; License 3156030919163, content publisher: Informa Healthcare, content publication: Annals of Human Biology)

Recent intensive environmental interventions by the Polish government have reduced emissions of harmful substances in areas with potential health hazards (Ignasiak et al., 2011). Interventions were targeted to maximize health-related benefits return on investment for the population resident in or close to the industrial zones (Bachowski et al., 2004). Observations from studies of the influence of elevated blood lead levels associated with industrial pollution in the Copper Basin on the growth, maturation and physical fitness of school children in the region have been conducted by Malina and colleagues (Ignasiak, Sławińska, Little).

The growth status, physical fitness and blood lead levels of school children, 7-15 years of age were surveyed in 1995 and 2007. Menarcheal status of girls was obtained by interview in both years. The children resided in seven communities (officially labeled villages) in the vicinity of major copper smelting and refinery facilities in the Legnica and Głogów districts. With two exceptions, schools in the same communities were surveyed in both years. Population sizes of the communities ranged from 337 to 1424 in 1995 and 266 to 1400 in 2007. All children were born and raised in the area. They were from families of mine and factory workers in the copper industry and farmers in the communities. The latter were largely part-time farmers with <10 hectares of land; most worked in the copper industry and only tended the farms after work and on weekends.

Relationships between blood lead levels and growth status are limited to the 1995 data (Ignasiak et al., 2006, 2007). Analyses of the 2007 data for growth status and physical fitness in the context of short-term secular change are currently under way. Changes in blood lead levels and ages at menarche between 1995 and 2007 have been analyzed (Ignasiak et al., 2011; Sławińska et al., 2012).

Growth Status

Reduced height was associated with elevated blood lead levels in school children of the Copper Basin observed in 1995 (Ignaziak et al., 2006). The negative effects of elevated blood lead were more apparent in growth of the extremities (arms, estimated leg length) than in growth of the trunk. Greater reductions in linear growth were observed at higher blood lead levels. The observations were consistent with experimental data suggesting a major influence of lead on linear bone growth, specifically proliferation of chondrocytes, hypertrophy and matrix calcification at the growth plates of long bones (Hicks et al., 1996). Other potential targets for lead are reduced osteoblast activity and bone remodeling (Puzas et al., 1992). It was deduced from these analyses that the effect of lead was on long bone growth than upon round bones (Ignasiak et al., 2006).

Physical Fitness

Relationships between blood lead levels and measures of physical fitness in the school were evaluated in the context of two research questions (Ignasiak et al., 2007). Are indicators of physical fitness directly related to blood lead levels? Alternatively, is physical fitness indirectly affected through reduced body size given the influence of elevated lead on linear growth? Smaller body size is generally associated with poorer performances on a variety of physical fitness tests in youth (Malina et al., 2004).

School children of both sexes from the Copper Basin in 1995 were on, average, shorter than Polish youth in a 1999 national physical fitness survey (Przewęda et al., 2005). Children from the Copper Basin also tended to weigh slightly less than the national sample between 7 and 11 years, while differences were negligible at older ages.

Several indicators of physical fitness were measured using the EUROFIT battery (Council of Europe, 1988): right and left grip (static strength), sit-ups in 30 seconds (abdominal muscular strength and endurance), flexed arm hang (upper body functional strength), plate tapping (speed of upper limb movement), shuttle run (running speed and agility), standing long jump (explosive power of the lower extremities) and medicine ball throw (explosive power of the upper extremities). Simple reaction time was measured in a subsample.

Standing long jump performances of boys and girls from the Copper Basin were, on average, slightly lower than those of the national sample from 7-13 years, while differences at 14-15 years were negligible. A similar age-related pattern was

apparent for speed of upper limb movement (plate tapping). Performances in an agility shuttle run did not differ, on average, between children of both sexes in the Copper Basin and the national sample. In contrast, the number of sit-ups completed in 30 seconds was consistently lower in Copper Basin children of both sexes across the age range 7-15 years. Grip strength was, on average, greater in boys and girls from the Copper Basin than in the national sample. However, this comparison must be tempered because it was not clear what type of dynamometer was used in the national survey.

Results of regression and path analyses indicated that blood lead level did not directly affect the physical fitness of the school youth from the Copper Basin (Ignasiak et al., 2007). The effects of blood lead on indicators of physical fitness were indirect through a negative influence of high blood lead on growth in body size. Blood lead level was also not related with reaction time in the subsample of children. However, diet and family circumstances (except for maternal education) and level of habitual physical activity were not considered. Nutritional status and familial factors can independently influence both growth and physical fitness, while physical activity is an important correlate of fitness (Malina et al., 2004).

Age at Menarche

Age at menarche and blood lead levels were considered in the two surveys of school girls separated by 12 years, 1995 and 2007 (Slawinska et al., 2012). Blood lead level and age at menarche (estimated with probit analysis) declined, on average, over this interval (Table 2). Logistic regression analyses were done for each year with menstrual status (0 = no, 1 = yes) as the dependent variable and with age, height (linear growth), BMI (weight-for-height), and lead group (binary variable, 0 = Pb $\leq$ 5.00 and 1= Pb $\geq$ 5.10 µg/dL) as the independent variables. The odds ratio for 1995 was not significant (p<0.48) indicating that lead group did not affect the odds of a girl attaining menarche. However, the odds ratio for 2007 approached significance (p=0.057). This indicates that increased blood lead was associated with later menarche (decreased odds of attaining menarche) in 2007.

Table 2. Blood lead levels and ages at menarche in school girls resident in the Copper Basin of Lower Silesia, Poland in 1995 and 2007.[1]

| Year | N | Blood Lead Level, µg/dL | | Age at menarche | |
		Mean	SE	Median	SD
1995	436	6.57	0.13	14.36	1.16
2007	346	4.24	0.14	12.73	1.22

[1]Adapted from Sławińska et al. (2012)

The major difference in the specific logistic regression analyses of the two time periods (1995 vs. 2005) was in the contributions of the covariate BMI and the main effect (blood lead group) to the probability of attaining menarche. The BMI was less important to attaining menarche in 2007 (OR = 1.18, 95% CI: 1.03-1.35) than in 1995 (OR = 1.51, 95% CI: 1.26-1.82). The opposite was true for lead, which had a smaller effect in 1995 (OR = 0.70, 95% CI: 0.27-1.85) than in 2007 (OR = 0.31, 95% CI: 0.09-1.06). It may be possible that the influence of blood lead on menarche in 1995 was through its effect on weight-for-height (BMI). The decline in age at menarche between 1995 and 2007 may thus reflect attenuation of multiple environmental stressors (chronic malnutrition, iron and calcium intake deficiencies) in addition to blood lead level. It may be possible that somewhat marginal nutritional and health conditions associated with unstable political, social and economic circumstances in Poland from the late 1970s through the 1980s (girls in the 1995 sample were born during this period) confounding the influence of lead on the process of sexual maturation in the 1995 sample such that a significant effect of lead on age at menarche was masked or diminished to statistically non-significant.

Observations for girls in the Copper Basin in 1995 beg the following question. Given the elevated blood lead levels in the sample, why was an association between lead levels and age at menarche not observed in 1995? The broad range of blood lead values (2.0-33.9 μg/dL) contributed to unusually wide 95% confidence intervals and in turn a non-significant association. A much larger sample size was likely needed to sufficiently power the 1995 analyses to detect the influence of lead level on menarcheal status to reach statistical significance.

However, comparisons of estimated ages at menarche in subsamples of girls with high (≥5.1 μg/dL) and low (≤5.0 μg/dL) blood lead levels in each year provide some insights. The difference between estimated median ages at menarche (probit analysis) for girls with high and low blood lead levels in 1995 was 0.35 years, while that between estimated medians ages in 2007 was 0.69 years, an effective doubling of the difference in the latter time period. The difference between estimates of menarcheal age in 1995 was slightly greater than that noted in rural girls with inadequate vs. adequate nutrition in the 1970s, 0.2 years (Charzewska et al., 1976). The secular decline between 1995 and 2007 was due in large part to a reduction in age at menarche in girls with low blood lead group in 2007 compared to girls with low blood lead in 1995 (0.49 years), while the difference in ages at menarche in girls with high lead in both years was small (0.15 years). This implies that other environmental conditions (i.e., nutritional) among girls with low blood lead levels (≤ 5μg/dL), improved more than among girls in the high blood lead level group. As suggested earlier, the effect of blood lead level seems confounded by socioeconomic variation, which apparently exerts a strong effect on age at menarche in the sample of Polish school girls who grew up before and after the fall of communism, 1995 and 2007 cohorts, respectively.

CONDITIONS IN POLAND

Synthesis of these data indicate that environmental and economic conditions of the 1980s (birth years of boys and girls in the 1995 survey) may be quite strong confounders in the relationship between blood lead level and sexual maturation and growth status. The decade between 1978 and 1988 in Poland was characterized by political turmoil and eventual changes (i.e., decline of communism) which had major economic and social consequences. National and regional surveys of the growth and maturation of Polish children and adolescents suggested unstable health and nutritional conditions in the 1970s and 1980s, i.e., prior to and during the turmoil associated with the fall of communism (Bielicki and Hulanicka, 1998). Inadequate nutrition indexed by regularity of meals, estimated intakes of specific nutrients and clinical symptoms of nutritional deficits were often noted in Poland during the 1970s, especially among children from rural areas and children of semiskilled manual workers (Konieczna, 1977).

Specific information on dietary calcium and iron (both of which are chemically similar to lead) in the villages surveyed in the Copper Basin during the 1980s and early 1990s is not available. Limited data indicated comparatively lower dietary intakes of calcium and iron than recommended in rural vs. urban adolescent Polish girls (Charzewska et al., 2006). It is reasonable to assume that the trends apply to girls resident in the villages surveyed in the Copper Basin. Among adolescents and young adults 13-25 years in Glogów and Lubin in 1995, dietary calcium approximated only 45% and 62% of recommended daily intake, respectively. Similarly, intakes of females relative to the norms were lower than those of males of the same age (Charzewska et al., 2006). Iron intakes of school girls in Glogów and Lubin in 1995 were, respectively, 64% and 75% of the recommended level. In contrast, corresponding estimates for boys were higher than recommended. Estimated iron intakes for random samples of girls 11-15 years resident in villages throughout Poland were 79% of recommended in 1995, while for random samples of girls 11-18 years in several specific regions of Poland in the late 1990s varied between 62% and 67% of recommended values (Charzewska et al., 2006). A synergistic interaction between lead levels and marginal nutritional conditions may explain the large but statistically not significant effect of elevated blood lead on menarche noted in the 1995 survey.

Differential effects of lead on linear growth and sexual maturation have also been suggested (Wu et al., 2003). Height of the total sample of girls and boys in the 1995 survey significantly decreased with increasing blood lead levels (Ignasiak et al., 2006). As noted, some experimental data have suggested an influence of lead on the proliferation of chondrocytes, hypertrophy and matrix calcification at the growth plates of long bones and in turn on linear bone growth (Hicks et al., 1996). Data from the 1995 survey parallel these experimental data, and suggest a greater effect of lead on long bone growth compared to round bones. Notably, lead effects on bone growth are cumulative over time. Menarche, in contrast, is a single point in time and ages at menarche based on status quo surveys (as in the surveys in the Copper Basin) are sample estimates. Specific information dealing with the

effects of elevated blood lead on neuroendocrine processes leading to delayed onset of menses is lacking, but available data suggest lead interrupts neuroendocrine functions. Marginal nutritional status and suboptimal calcium and iron intakes may be exacerbate factors that confound the influence of elevated lead on menarcheal status. These effects may operate through socioeconomic status, which is known to be highly correlated with blood lead levels (Ballew et al., 1999).

It is clear that improved health, nutritional and general living conditions, decreased environmental exposure to lead and better socioeconomic conditions in the Copper Basin between 1995 and 2007 contributed to a reduction in the age at menarche. It is difficult, however, to partition the secular decline in age at menarche associated with improved living conditions from the decline in blood lead levels between 1995 and 2007. As noted earlier, the analysis of secular change in growth status is currently in process.

An indicator of maturity status was not available for boys from the Copper Basin. It is reasonable to assume similar secular changes among males because blood lead levels also declined significantly in boys (Ignasiak et al., 2011). Importantly, percentages of youth with blood lead levels ≥ 6 µg/dL were higher in boys than girls in both years (1995, 77% vs 52%; 2007, 33% vs 17%). However, it is important to note that Poland instituted a requirement for catalytic converters on all cars produced since 1995, and this has contributed to the decrease in blood lead levels. But the magnitude of the contribution of this to decreased blood lead levels is unknown.

Unfortunately, data on uptake of lead and other toxicants by food crops grown in lead-tainted soil and perhaps on the nutrient quality of crops were not available. Moreover, other potential toxicants in the blood were not considered. In addition to lead, age at menarche was sensitive to several polychlorinated biphenyl (PCBs) congeners in a sample of Akwesasne Mohawk girls described earlier (Denham et al., 2005). On the whole, the results highlight the need to expand future studies to include simultaneous analysis of other toxicants that may influence the process of sexual maturation, growth, and development.

CONCLUSIONS

In 2012 the United States Centers for Disease Control and Prevention (CDC) lowered the blood lead level for medical intervention in children from 10 µg/dL to 5 µg/dL (American Academy of Pediatrics, 2012). This was a welcome change as it is clear from human investigations that adverse effects on growth and sexual maturation are detectable at blood lead levels <10 µg/dL. Children in the Polish Copper Basin (Lower Silesia) have responded in an expected fashion to reduced environmental lead burden. The question remains, however, whether or not lead effects are a threshold effect or a dose-response effect. Most data suggest there may be no safe level for lead as there is no safe level for mercury for developing children. Minamata disease/syndrome was not documented until 1956 although

mercury had been used by humans medicinally and cosmetically since at least 1500 B.C. Continued vigilance is prudent for known toxic elements such as lead.

It is extremely important for medical and policy professionals to fully appreciate the implications of environmental lead exposure. National and individual social and economic development cannot proceed at optimal levels when significant portions of the population suffer from lead-induced growth and neurodevelopmental impairments. Physical and mental impairments are associated with even low levels of lead (>5 μg/dL, American Academy of Pediatrics, 2012) which can potentially impede individual and national progress due in part to stunted physical growth and intellectual deficits. With environmental lead pollution, otherwise normal children are destined to suffer poor outcomes (growth stunting, delayed maturation) when environmental lead is not controlled through aggressive, effective abatement programs. In Poland, reduced smelter emissions of lead, transition to catalytic converters, and use of unleaded gasoline have had a significant biological benefit for growth and health of children. The national economic forecast is thus much more optimistic than in the past because the workforce has been improved physically and mentally through the improvement of childhood growth and maturation.

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