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Lead exposure is associated with a delay in the onset of puberty in South African adolescent females: Findings from the Birth to Twenty cohort

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ABSTRACT

Introduction: One of the suggested, yet under-researched, causes of pubertal delay is lead exposure. In South Africa blood lead levels are generally higher than in resource-rich countries. Thus the effects of lead exposure on pubertal development may be significant.
Objective: The objective of this study is to determine the association between lead exposure and pubertal development in adolescent females in the Birth to Twenty cohort (Bt20).
Methods: Bt20 is a Johannesburg based birth cohort study that commenced in 1990 and includes 1682 girls. At 13 years of age venous blood samples were collected from 725 adolescent female participants for lead content analyses; of these, 712 had menarche data. Pubertal measurement was based on age of menarche and self-reported Tanner staging for pubic hair ($n=684$) and breast development ($n=682$).
Results: The mean blood lead level for the sample was 4.9 μg/dl. Fifty percent had blood lead levels <5.0 μg/dl, 49% were ≥5.0 μg/dl and 1% was >10.0 μg/dl. The average age of menarche was 12.7 years. At 13 years, 4% and 7% had reached Tanner stage 5 for pubic hair and breast development, respectively. Analyses showed that higher blood lead levels were associated with significant delays in the onset of puberty ($p<0.001$).
Conclusion: The study found that higher blood lead levels were associated with a delay in the onset of puberty, after adjustment for confounders. Lead exposure in resource-poor countries is generally higher compared to resource-rich countries and thus the effects of high blood levels have personal and public health significance.

1. Background

Blood lead levels have been decreasing across the world, especially in resource-rich countries where blood lead levels now average around 3 μg/dl or lower (Koller et al., 2004; Harper et al., 2003). However, in low and middle income countries elevated blood lead distributions continue to be widespread because of the ongoing use of lead in the informal and formal sectors (Fewtrell et al., 2004; Falk, 2003; Tong et al., 2000). Poor children are among the worst affected. In 1995, Johannesburg school children aged 6 to 7 years were found to have a mean blood lead level of 12.0 μg/dl (Mathee et al., 2004). By 2002, the mean blood lead level in a repeat study involving children from the same schools had declined somewhat to 9.1 μg/dl (Mathee et al., 2004), but was still decidedly above international levels. Lead exposure in South Africa thus continues to be a significant public health problem.

The detrimental health effects of lead at high and even relatively low levels are well established in children both in terms of physical development and mental health. Elevated lead levels have been associated with impaired neurological development and behavioural problems such as hyperactivity and delinquent behaviour as well as renal and haematological abnormalities (Bellinger et al., 1994; Dietrich et al., 2001; Needleman et al., 2002; Lin et al., 2003; Cheng et al., 2001). At blood lead levels as low as 3.0 μg/dl significant detrimental health effects have also been found, including intellectual deficits and behavioural abnormalities (Lanphear et al., 2005; Bellinger, 2004; Canfield et al., 2003; Bernard, 2003).

One of the suggested effects of lead exposure is a delay in the onset of puberty. Animal models have shown that lead affects the endocrine system, possibly through disrupting hypothalamic or pituitary function, and/or direct action at peripheral sites such as the gonads (Winder, 1989; Klein et al., 1994; Wiebe et al., 1982; Huseman et al.,

Abbreviations: BLL, Blood lead levels; BMI, Body Mass Index; Bt20, Birth to Twenty; WHO, World Health Organization; μg/dl, micrograms per decilitre.

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1992; Camoratto et al., 1993). Animal studies have also shown an association between blood lead and delayed puberty (Ronis et al., 1998; Dearth et al., 2002). However, only a few human studies have looked at the impact of lead on pubertal development (Wu et al., 2003; Selevan et al., 2003; Denham et al., 2005). Nonetheless, all studies report an association between low level lead exposure and pubertal delay. To our knowledge, all of the published studies have been conducted in resource-rich countries.

There is a dearth of information on the impacts of lead levels in resource-poor countries, including South Africa. The objective of this study was to determine the association between lead exposure and pubertal development in female adolescents living in Johannesburg, South Africa.

2. Materials and methods

2.1. Study design and sampling

The Birth to Twenty (Bt20) study is a longitudinal birth cohort study. The study commenced in 1990 in the metropolitan area of Johannesburg/Soweto, South Africa. Inclusion into the study occurred if participants were born between April and June 1990, and if their mother lived in the Johannesburg/Soweto area for at least 6 months after delivery (n = 3273). The cohort enrolment and attrition is well described in several publications (Yach et al., 1990; Richter et al., 2004; Norris et al., 2007; Richter et al., 2007). The study aimed to assess the socio-economic, environmental, development, health and overall well-being of the participants.

The Bt20 has a total of 1682 female participants. Of these, 1529 were Black and Mixed ancestry adolescent females. White and Indian females were excluded because of their small numbers. Of these, 725 had venous blood collected for lead analyses at the 13 year data collection wave; 804 participants did not have blood lead levels for a variety of reasons, including not providing consent for a blood draw, a small number of blood samples were not suitable for lead concentration analyses, some participants still in contact with the study did not present at the data collection site, and participants lost due to study attrition. Of the 725 participants with blood lead data, 712 had data on the onset of menarche, 684 had pubic hair Tanner staging data and 682 had breast staging data. The sample included in the current analysis is illustrated in Fig. 1; 682 cases were available for the analysis (Fig. 1).

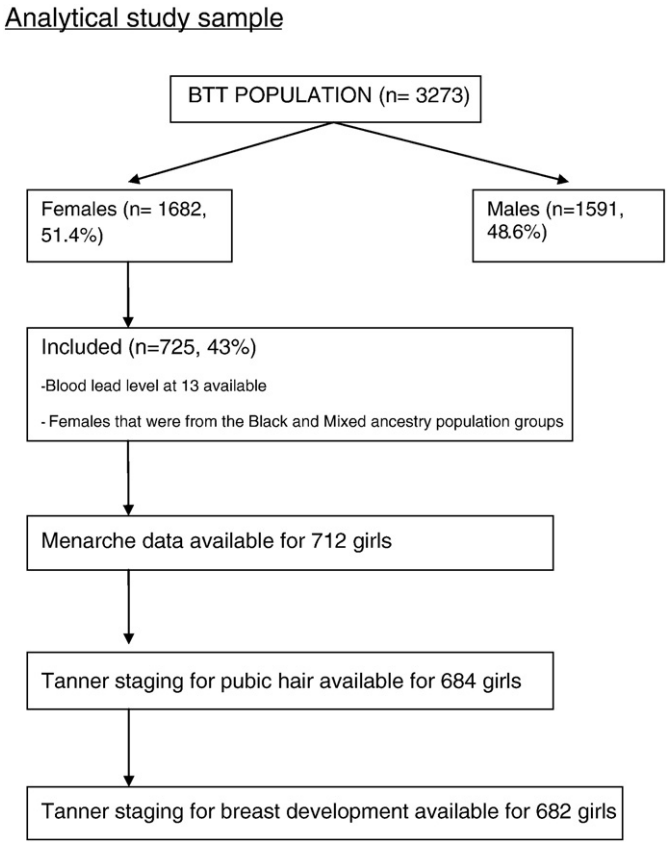

Fig. 1. Sample included in current analysis.

2.2. Procedures/data collection

During the data collection wave when the participants were 13 years of age, pubertal development was assessed on the basis of reported age of menarche and Tanner staging for pubic hair and breast development. Self-reported pubertal staging was used to assess pubertal development, using procedures previously validated among the cohort (Norris and Richter, 2005, 2008). Anthropometric measurements (weight and height) were taken and Body Mass Index (BMI) calculated. In addition, whole venous blood was collected into heparinised tubes free of trace metals. Following preparation and centrifugation, lead concentrations in the whole blood samples were determined using an atomic absorption spectrophotometer equipped with a graphite furnace. Blood lead measurements were performed by the South African National Institute for Occupational Health. The laboratory is part of an international and national quality control programme for blood lead analyses (Röllin et al., 1988).

2.3. Data analysis

Demographic data, maternal education, and socio-economic status collected on the cohort were utilised in the analyses.

The blood lead level was the exposure variable. Blood lead levels ranged from 1.04 to 16.25 μg/dl. Lead levels were not normally distributed; however log transformation did not influence the results. There were no differences between Black females and those of Mixed ancestry. The mean blood lead level for Black females was 4.99 μg/dl and for Mixed ancestry females it was 4.66 μg/dl.

Sexual maturation as measured by attainment of menarche and Tanner staging of pubic hair and breast development were the outcome variables. Tanner staging for breast development and pubic hair was classified into five stages with stage one being the most immature and stage five equalling pubertal attainment. The trends in sexual maturation did not differ between Black and Mixed ancestry participants.

Means and proportions were used to describe the study population. Trend analyses for mean lead levels and pubertal factors were conducted. For logistic regression analyses, blood lead levels were dichotomised at 5.0 μg/dl: 4.9 μg/dl and below and 5.0 μg/dl and above. The level of 5.0 μg/dl was used because it was close to the mean blood lead level of 4.9 μg/dl and was also based on international discussions regarding changing of the action level for blood lead from 10.0 μg/dl to 5.0 μg/dl (Gilbert and Weiss, 2006). The attainment of menarche and attained Tanner stage across the dichotomised blood lead categories was adjusted for socio-economic status and anthropometric measures. The onset of menarche and Tanner stage served as dependent variables, and blood lead levels were fitted into logistic regression models to test their associations with them. All statistical tests were conducted using the STATA 9 statistical package. Statistical significance was determined at a level of $p<0.05$.

2.4. Ethics

Ethical approval for the study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand in