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Prenatal lead exposure and childhood blood pressure and kidney function

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ABSTRACT

Background: Exposure to lead, a common environmental pollutant, is known to cause cardiovascular and nephrotoxic effects in adults. Potential effects of early-life lead exposure on these functions are, however, less well characterized.
Objectives: To assess blood pressure and kidney function in preschool-aged children in relation to prenatal lead exposure.
Methods: This prospective study in rural Bangladesh measured children's systolic and diastolic blood pressure in triplicate at the follow-up at 4.5 ± 0.11 years. Their kidney function was assessed by the estimated glomerular filtration rate (eGFR), calculated based on serum cystatin C concentrations, and by kidney volume, measured by sonography. Exposure to lead was assessed by concentrations in the mothers' blood (erythrocyte fraction; Ery-Pb) in gestational weeks (GW) 14 and 30, the effects of which were evaluated separately in multivariable-adjusted linear regression analyses.
Results: We found no associations between maternal exposure to lead [n ~ 1500 for GW14 and 700 for GW30] and children's blood pressure or eGFR. However, we found an inverse association between late gestation lead and kidney volume, although the sample size was limited (n = 117), but not with early gestation lead (n = 573). An increase of 85 μg/kg in Ery-Pb (median concentration at GW30) was associated with a 6.0 cm^3/m^2 decrease in kidney volume (= 0.4 SD; p = 0.041). After stratifying on gender, there seemed to be a somewhat stronger association in girls.
Conclusions: Prenatal lead exposure may cause long-lasting effects on the kidney. This warrants follow-up studies in older children, as well as additional studies in other populations.

1. Introduction

Lead is one of the most toxic chemicals for the developing organism, and it is commonly present in soil, dust, certain food items, and various household products (EFSA, 2013; NTP, 2012). Lead readily passes the placenta and reaches the fetus, where it may impair brain development and intrauterine growth even at very low exposure levels (Boucher et al., 2014; EFSA, 2013; Taylor et al., 2014). In adults, chronic lead exposure has been related to impaired kidney function and cardiovascular disease (CVD; EFSA, 2013; Pollack et al., 2015; Spector et al., 2011), the latter being the leading cause of death in the world (Lim et al., 2012). Increased blood pressure has been positively associated with the risk of stroke and coronary heart disease, and raised blood pressure has been estimated to cause around 13% of all annual deaths (WHO, 2010). The majority of the risk factors for CVD are modifiable, such as environmental exposure to metals like lead, but still the prevalence of CVD in low- and middle income countries is increasing (WHO, 2010).

Recent studies suggest that the pre- or perinatal period might be a critical window of exposure also for subsequent lead-induced cardiovascular effects. In a Mexican study, maternal tibia lead concentrations were found to be positively associated with blood pressure in their children (n = 457) at 7–15 years of age (Zhang

Abbreviations: As, arsenic; BP, blood pressure; Cd, cadmium; BAZ, BMI for age z-score; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; Ery-Pb, erythrocyte lead; GW, gestation week; GP6, glycoprotein VI; HAZ, height for age z-score; icddr,b, International Centre for Diarrhoeal Disease Research, Bangladesh; ICPMS, Inductively coupled mass spectrometry; LOD, limit of detection; MINIMat, Maternal and Infant Nutrition Interventions, Matlab; SES, socioeconomic status; WAZ, weight for age z-score; WHZ, weight for height z-score

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et al., 2012), and in the US, cord blood lead concentrations were associated with blood pressure in 9-year old children (N=122) (Gump et al., 2005). Similarly, experimental studies in rats have shown elevated blood pressure in offspring to lead-exposed dams (Gaspar and Cordellini, 2014).

There is increasing evidence that stressors early in life may increase the risk of health effects much later in life (Barker et al., 2005; Dasinger and Alexander, 2016), likely partly through epigenetic mechanisms operating during critical periods of development. The observed late effects of prenatal lead exposure on blood pressure may therefore imply a prenatal programming effect on later life cardiovascular disease risk factors. Indeed, we recently found that early prenatal lead exposure was associated with lower DNA methylation in the promoter region of a cardiovascular-related gene, glycoprotein VI (*GP6*), and that this effect seemed to remain until preschool-age (Engström et al., 2015). As the activating platelet collagen receptor glycoprotein VI is involved in pathological thrombus formation and related inflammatory processes (Dutting et al., 2012), we hypothesized that an altered programming by early-life lead exposure may be linked to cardiovascular disease later in life. In the present study, we test this hypothesis by evaluating the impact of prenatal lead exposure on children's blood pressure and kidney function at preschool-age.

2. Subjects and methods

2.1. Study area and population

The present study is part of the follow-up of the MINIMat (Maternal and Infant Nutrition Interventions, Matlab) trial, a food and multi-micronutrient supplementation trial in pregnancy, conducted in rural Bangladesh by the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), as described elsewhere (Persson et al., 2012). The criteria for enrollment into the trial were viable fetus, gestational age less than 14 weeks by ultrasound examination, no severe illness, and written consent for participation. Women were randomized into six groups with either early [from gestational week (GW)9] or usual (from GW20) food supplementation, together with 30 or 60 mg of iron and 400 μg of folic acid, or a multimicronutrient tablet containing the daily allowance of 15 micronutrients (from GW14). Early in the study we discovered that elevated exposure to arsenic through drinking water was common in this area, and therefore we initiated a longitudinal research project to evaluate potential developmental effects of arsenic and other environmental pollutants (Bergkvist et al., 2010; Gardner et al., 2013).

The follow-up of the children born in the MINIMat trial at 4.5 years of age included children born June 2002-June 2004 (n=2499; Hawkesworth et al., 2013a). In the present study, we included mother-child pairs that overlapped with our previous studies on exposure to toxic metals, including the mothers' lead exposure measured either at GW14 (second trimester) or GW30 (third trimester; Fig. 1). The recruitment to these studies (January 2002–April 2003) has been described in detail previously (Li et al., 2008; Rahman et al., 2013; Hamadani et al., 2010; Skröder et al., 2015a). These women had children born into the trial August 2002-December 2003. In total, this new cohort consisted of 1699 mother-child pairs with Ery-Pb measured at GW14, and 746 mother-child pairs with Ery-Pb measured at GW30. We excluded 176 pairs because they included twins or missed covariate information (Fig. 1). Two women had unreasonably high Ery-Pb concentrations (607 μg/kg at GW14 and 850 μg/kg at GW30). As these concentrations were around twice as high as the second highest concentration in each gestational week, and since both women had much lower concentrations at the other sampling point, we cannot exclude contamination. Finally, these values had disproportional influence on the results, and were thus excluded from the new cohort. Out of the remaining participants, we had all available characteristics and Ery-Pb measured at GW14 for 1511 mother-child pairs, and for 713 pairs at GW30 (Fig. 1). In total, 658 women had blood analyzed for lead at both time points (GW14 and 30).

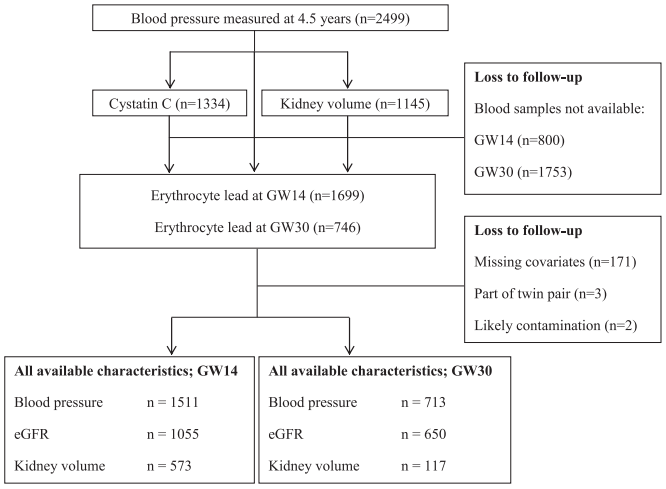

Fig. 1. Flow chart showing the recruitment into the present study. Abbreviations: eGFR, estimated glomerular filtration rate; GW, gestational week.

Included women had similar Ery-Pb concentrations at GW14 (median 73 μg/kg) as the excluded women (median 76 μg/kg). Children with maternal lead data were marginally younger (mean 4.5 *vs* 4.6 years old), had slightly more siblings (mean 1.4 *vs* 1.3), larger kidney volume (mean 107 *vs* 100 cm^3/m^2), lower systolic blood pressure (mean 91 *vs* 92 mmHg), higher estimated glomerular filtration rate (eGFR; mean 92 *vs* 89 ml/min/1.73 m^2), and belonged to families with a lower socioeconomic status (SES; mean −0.12 *vs* 0.11; but the range was the same, −5.9–4.0), compared to those who lacked measurements of their prenatal lead exposure (p for all <0.05). Although statistically significant, these differences were at the most 8%.

The project was approved by the research and ethical review committees at icddr,b and the ethical committees at Uppsala University, Uppsala, and Karolinska Institutet, Stockholm, Sweden. The study was conducted in accordance with the Helsinki Declaration. The women gave written consent at recruitment, and parents or other guardians gave their written consent prior to the children's enrollment at the 4.5 years follow-up study (Hawkesworth et al., 2013b).

2.2. Exposure assessment

Prenatal exposure was assessed through lead concentrations in maternal blood (erythrocyte fraction) in early (GW14) and late (GW30) pregnancy (Bergkvist et al., 2010). Maternal blood was collected at the health clinics using 5.5 ml lithium-heparin tubes (tested free from trace elements of interest for the study) and transported to the hospital lab for separation of plasma and erythrocytes. All samples were stored frozen until analyzed at Karolinska Institutet, Sweden. Erythrocyte lead (Ery-Pb) at GW14 was analyzed using inductively coupled mass spectrometry (ICPMS) following dilution of 1:25 in an alkali solution [2% (w/v)1-butanol, 0.05% (w/v) EDTA, 0.05% (w/v) Triton X-100, 1% (w/v) NH_4OH and 20 μg/L internal standard] (Lu et al., 2015). The LOD was <0.015 μg/L, and no samples were below this limit. The quality control of the ICPMS analyses was performed by analyzing