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Kidney function and blood pressure in preschool-aged children exposed to cadmium and arsenic - potential alleviation by selenium

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ABSTRACT

Background: Early-life exposure to toxic compounds may cause long-lasting health effects, but few studies have investigated effects of childhood exposure to nephrotoxic metals on kidney and cardiovascular function.
Objectives: To assess effects of exposure to arsenic and cadmium on kidney function and blood pressure in pre-school-aged children, and potential protection by selenium.
Methods: This cross-sectional study was part of the 4.5 years of age (range: 4.4–5.4 years) follow-up of the children from a supplementation trial in pregnancy (MINIMat) in rural Bangladesh, and nested studies on early-life metal exposures. Exposure to arsenic, cadmium and selenium from food and drinking water was assessed by concentrations in children's urine, measured by ICP-MS. Kidney function was assessed by the estimated glomerular filtration rate (eGFR, $n=1106$), calculated from serum cystatin C, and by kidney volume, measured by ultrasound ($n=375$). Systolic and diastolic blood pressure was measured ($n=1356$) after five minutes rest.
Results: Multivariable-adjusted regression analyzes showed that exposure to cadmium, but not arsenic, was inversely associated with eGFR, particularly in girls. A 0.5 μg/L increase in urinary cadmium among the girls (above spline knot at 0.12) was associated with a decrease in eGFR of 2.6 ml/min/1.73 m^2, corresponding to 0.2SD ($p=0.022$). A slightly weaker inverse association with cadmium was also indicated for kidney volume, but no significant associations were found with blood pressure. Stratifying on children's urinary selenium (below or above median of 12.6 μg/L) showed a three times stronger inverse association of U-Cd with eGFR (all children) in the lower selenium stratum (B = −2.8; 95% CI: −5.5, −0.20; $p=0.035$), compared to those with higher selenium (B = −0.79; 95% CI: −3.0, 1.4; $p=0.49$).
Conclusions: Childhood cadmium exposure seems to adversely affect kidney function, but not blood pressure, in this population of young children in rural Bangladesh. Better selenium status appears to be protective. However, it is important to follow up these children to assess potential long-term consequences of these findings.

1. Introduction

Evidence of developmental programming of non-communicable diseases, including chronic kidney disease (CKD) is increasing steadily (Luyckx et al. 2013; Maringhini et al. 2010). An abnormal early-life development of the kidneys, particularly a decreased nephron number, may clinically manifest as CKD later in life, which in turn may lead to cardiovascular disease (Luyckx et al. 2013). The kidney is a target organ for multiple toxic chemicals, including arsenic and cadmium (Jarup and Akesson 2009; Madden and Fowler 2000; Zheng et al. 2014). Children may be considered a high-risk group, since the developing kidney is particularly susceptible to nephrotoxic agents (Suzuki 2009; Trzcinka-Ochocka et al. 2004). Also, children are exposed to more water and food pollutants per kg body weight than adults (Schoeters et al. 2006; Valent et al. 2004), and have a high absorption rate of several metals, including cadmium, in the gastrointestinal tract (de

Abbreviations: BAZ, BMI for age z-score; BUN, blood urea nitrogen; CKD, Chronic kidney disease; eGFR, estimated glomerular filtration rate; GW, gestational week; HAZ, height for age z-score;icddr; b, International Centre for Diarrhoeal Disease Research, Bangladesh; ICP-MS, Inductively coupled mass spectrometry; MINIMat, Maternal and Infant Nutrition Interventions, Matlab; U-As, Urinary arsenic; U-Cd, Urinary cadmium; U-Se, Urinary selenium; WAZ, weight for age z-score; WHZ, weight for height z-score.

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Burbure et al. 2003; Kippler et al. 2010).

There are, however, few studies evaluating potential kidney effects of early-life exposure to arsenic and cadmium. A recent study in Chile indicated increased mortality from CKD in young adults following *in utero* and childhood exposure to arsenic via drinking water (Smith et al. 2012). We have previously shown that exposure to arsenic, but not cadmium, during pregnancy and at 18 months of age was associated with increased diastolic blood pressure in rural Bangladeshi children at 4.5 years of age (Hawkesworth et al. 2013b). Because of the persistent exposure to arsenic via drinking water and food in the study area, in spite of ongoing mitigation efforts (Gardner et al. 2011), the objective of the present study was to follow up these children and evaluate if the continuous exposure during preschool-age, caused a progression of the observed effects on blood pressure, and possibly also on kidney function. We also evaluated potential associations with cadmium, since it accumulates in the kidneys, and as we found that these children, living in a rural area, had unexpectedly high cadmium exposure (Kippler et al. 2010). Also, cadmium exposure has previously been associated with impaired renal function in children (de Burbure et al. 2006).

Different types of kidney diseases are often associated with low selenium status (Iglesias et al. 2013), although it is not entirely clear whether this is a cause or an effect of the disease. It has been proposed that selenium can protect against the toxic effects of pro-oxidant metals, such as arsenic and cadmium, (Madden and Fowler 2000; Zwolak and Zaporowska 2012), and we therefore assessed the possibility of selenium working as an effect modifier when exploring associations of arsenic and cadmium with kidney and cardiovascular function in the present study.

2. Subjects and methods

2.1. Study area and population

The present cross-sectional study is a part of the follow-up of the MINIMat (Maternal and Infant Nutrition Interventions, Matlab) food and multi-micronutrient supplementation trial in pregnancy, conducted in Matlab, rural Bangladesh. The trial was carried out by the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) as described elsewhere (Persson et al. 2012; Tofail et al. 2008). All women recruited to the trial were randomized into two different food groups [early (Gestational Week [GW]9) or usual (GW20) invitation] and three different micronutrient supplementation groups (30 mg iron and 400 μg folic acid; 60 mg iron and 400 μg folic acid; or multiple micronutrients), resulting in a total of six groups. Because it was discovered at an early stage that an elevated exposure to arsenic (through well water, the main source of drinking water) and cadmium (through rice, the main staple food) was common in this area, we added a longitudinal research project to evaluate potential developmental effects of these pollutants (Gardner et al. 2013; Kippler et al. 2012b; Vahter et al. 2006). In total, there were 3267 singleton live births in the MINIMat trial, and out of these children, 2499 were available for follow-up at 4.5 years of age. As described in detail elsewhere (Hawkesworth et al. 2013b), all these children had their blood pressure measured, whereas two different measures of kidney function (Cystatin C for calculation of eGFR and kidney volume) were conducted in two different sub-samples ($n=1334$ and $n=1145$, respectively; Fig. 1), mainly to minimize the participant burden but also to reduce the cost. In short, children without measurements of kidney function and blood pressure did not differ markedly from those with these functions assessed (Hawkesworth et al. 2013b). The present follow-up of concurrent exposure to arsenic, cadmium and selenium in relation to kidney and cardiovascular function consisted of those children who had the concentrations of these elements measured in urine at 5 years of age (born June 2002–June 2004; $n=1715$), and data available on general characteristics (Fig. 1; Table 1).

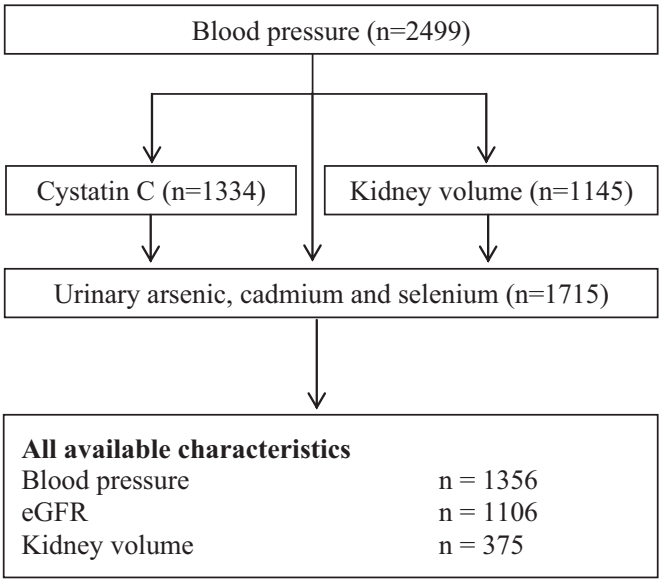

Fig. 1. Flow diagram of recruitment into the present study.

The project was approved by the research and ethical review committees at icddr,b, Bangladesh and the Ethical Committee at the Karolinska Institutet, Sweden. The study was conducted in accordance with the Helsinki Declaration. The parents or other guardians gave their written consent prior to the children's enrollment (Hawkesworth et al. 2013b).

2.2. Exposure assessment

Children's urine samples were collected a few months after assessment of kidney function (on average 8 months later), when they were about 5 years of age (mean ± SD: 5.2 ± 0.2 years). Although the concentration of metabolites of inorganic arsenic in urine (U-As) reflects ongoing exposure (Vahter 2002), we found that the exposure through drinking water and food in this area was fairly constant over time (Gardner et al. 2011), supporting that U-As also reflects long-term exposure. The urinary concentration of cadmium (U-Cd) reflects the concentration in the kidneys, and is a recognized marker of long-term exposure (Jarup and Akesson 2009). Since the major route of excretion for selenium is via urine, urinary selenium (U-Se) has been suggested as a useful marker of selenium status, especially in populations with low selenium intake (Szybinski et al. 2010), which is the case in the present cohort (Skröder et al., 2014).

Urine samples were collected in containers tested previously and found to be metal-free (unpublished data), and thereafter transferred to 24 mL acid-washed polyethylene containers by trained community health research workers (Gardner et al. 2011). We were not able to collect mid-stream urine from the children, and therefore we had to be observant on potential contamination. All samples were stored frozen during transport to Sweden and before analyzes at Karolinska Institutet, Sweden. We analyzed the metabolites of arsenic (inorganic arsenic, methylarsonic acid and dimethylarsinic acid) using high pressure liquid chromatography with on-line hydride generation (HPLC-HG) and inductively coupled plasma mass spectrometry (ICP-MS; As^{75}), with appropriate quality control (Gardner et al. 2011; Gardner et al. 2013). The sum concentration (inorganic arsenic+ methylarsonic