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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.

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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).

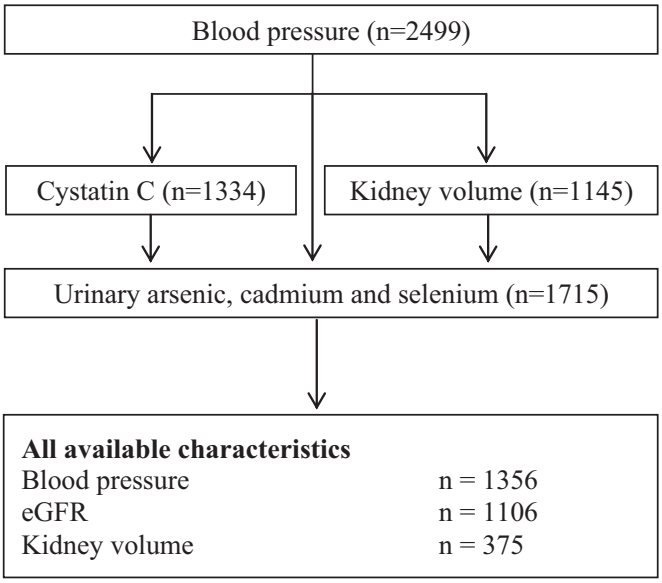

Fig. 1. Flow diagram of recruitment into the present study.

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

Table 1
Characteristics of the studied children and their mothers, as well as urinary concentrations of arsenic, cadmium and selenium, by outcome groups.

	Blood pressure ($n=1356$)	eGFR ($n=1106$)	Kidney volume ($n=375$)
	Mean ± SD[a]	Mean ± SD[a]	Mean ± SD[a]
Mothers			
Age (years)	27 ± 6.0	27 ± 6.0	26 ± 6.1
BMI in early pregnancy (kg/m^2)	20 ± 2.5	20 ± 2.6	20 ± 2.6
Parity	1.5 ± 1.4	1.5 ± 1.4	1.5 ± 1.5
Children			
Sex (% male/female)	53/47	53/47	53/47
Age at outcome measurement (years)	4.5 ± 0.11	4.5 ± 0.11	4.5 ± 0.062
Birth weight (g)	2687 ± 397	2686 ± 397	2715 ± 395
Weight (kg)	14 ± 1.7	14 ± 1.6	14 ± 1.6
Weight for age (z-score)	−1.8 ± 0.87	−1.8 ± 0.86	−1.7 ± 0.83
Height (cm)	99 ± 4.3	99 ± 4.4	99 ± 4.1
Height for age (z-score)	−1.5 ± 0.95	−1.5 ± 0.95	−1.6 ± 0.91
Weight for height (z-score)	−1.3 ± 0.81	−1.3 ± 0.82	−1.2 ± 0.78
Cystatin C (mg/L)	0.85[b] ± 0.11	0.85 ± 0.11	–
eGFR (ml/min/1.73 m^2)	92[b] ± 12	92 ± 12	–
Kidney volume[c](cm^3/m^2)	108[d] ± 16	–	108 ± 16
Systolic BP (mm Hg)	91 ± 8.0	91[b] ± 7.9	93 ± 8.5
Diastolic BP (mm Hg)	54 ± 6.7	54[b] ± 6.8	55 ± 6.6
Urinary arsenic (μg/L)[a, e]	54 (16–343)	51 (16–364)	55 (17–285)
Urinary cadmium (μg/L)[a, e]	0.22 (0.078–0.63)	0.22 (0.080–0.63)	0.21 (0.083–0.64)
Urinary selenium (μg/L)[a, e]	13 (6.2–26)	13 (6.0–26)	13 (7.1–27)

BP, blood pressure; eGFR, estimated glomerular filtration rate.

[a] For skewed variables, median (5–95th percentile) is presented.
[b] $n=1096$ (children with both blood pressure and eGFR measured)
[c] Adjusted for body surface area calculated from the Haycock formula (Haycock et al. 1978).
[d] $n=369$ (children with both blood pressure and kidney volume measured)
[e] Adjusted for variation in urine dilution by specific gravity (mean 1.012); [element concentration (μg/L)] × (1.012 − 1)/[measured specific gravity − 1].

acid + dimethylarsinic acid, all in μg/L) was used as measure of exposure. Concentrations of cadmium and selenium in urine were measured with ICP-MS (Agilent 7700x, Agilent Technologies, Tokyo, Japan) equipped with an octopole reaction system (ORS) to minimize spectral interferences. Cadmium[111] was measured in helium mode with iridium[193] as internal standard, whereas selenium[78] was measured in hydrogen mode with germanium[72] as the internal standard. The external calibration curve for cadmium ranged from 0 to 10 μg/L, and that for selenium from 0 to 100 μ/L. The standard solution for the external calibration of cadmium and selenium was prepared daily in 1% nitric acid (diluted volume to volume from 65% suprapur; Merck, Darmstadt, Germany) from a stock standard (Multi-element standard solution VI for ICP-MS Certipur®, Merck, Darmstadt, Germany). The urine samples were diluted 1:10 in 1% nitric acid (Merck, Darmstadt, Germany). The quality control of the ICP-MS analyzes for cadmium has been reported previously (Gardner et al. 2013). That of selenium included commercial reference materials for urine (Seronorm TM Trace Elements Urine; LOT OK4636 and LOT NO2525). The obtained values (24 ± 1.9 and 73 ± 4.6 μg/L, respectively) were in agreement with reported values (18.9–24.5 and 59.8–74 μg/L, respectively). No sample was below the LOD for any of the elements.

In order to account for variation in urine dilution, the measured urinary concentrations of arsenic, cadmium and selenium were adjusted to the average specific gravity (1.012), using the equation [element concentration (μg/L)] × (1.012 − 1)/(measured specific gravity) (Nermell et al. 2008). The specific gravity was measured with a URICON-NE refractometer (Atage Co. Ltd., Tokyo, Japan). We chose specific gravity rather than creatinine since we previously found this adjustment to be more suitable in the present population due to the high prevalence of malnutrition. Adjusting for creatinine would result in overestimation of the urinary element concentrations in the most malnourished individuals with low urinary creatinine concentrations. The urine adjustment method is sometimes discussed as potentially influential for associations between urinary biomarkers and kidney related outcomes (Weaver et al. 2014). Osmolality has been suggested as a useful adjustor since this is less affected by the size of the molecules, compared to the specific gravity. Analysis of osmolality in a subsample ($n=30$) showed a spearman correlation of 0.98 ($p<0.001$) with the specific gravity in the present population.

2.3. Outcome assessment

Children's blood pressure was measured in triplicate using an automated oscillometric device (Omron 705IT, Morton Medical) (Hawkesworth et al. 2013a). These measurements were performed by trained field workers at the health care facilities run by icddr,b. The first measurement was taken after the child had been seated at rest for five minutes. Subsequent measurements were taken at one minute intervals, and the mean blood pressure from these three readings was calculated. To assess kidney function, the eGFR was calculated using plasma cystatin C, which was analyzed in stored, frozen plasma samples with the immunoturbidimetric method at Uppsala University Hospital, Sweden (Flodin et al. 2007). A prediction equation developed based on Swedish patients and applicable for use in children (Grubb et al. 2005) was initially used to calculate eGFR from the cystatin C concentration [eGFR {mL min^{-1} (1.73 m^2)$^{-1}$}$=84.69 \times$ cystatin C (mg/L)$^{-1.680} \times 1.384$] (Hawkesworth et al. 2013b). Because this equation gave unexpectedly high eGFR values, we used the equation developed by Hoek [eGFR$=-4.32+80.35 \times$ cystatin C (mg/L)$^{-1}$] for the present study, as that was recently evaluated as a useful cystatin C based equation for use in children (Zachwieja et al. 2014). Measurements of kidney volume (cm^3/m^2) by ultrasonography (3.75 MHz, convex scanner; Toshiba SSA- 510 A/P3, Famio-5, Toshiba Medical Systems) were conducted by physicians after extensive training and standardization. Right and left kidney volumes were calculated using internal software that turns a best-fit ellipsoid shape into an estimate of volume. The mean right and left kidney volume was

then adjusted for body surface area calculated from the Haycock formula; surface area (m^2) = weight $(kg)^{0.5378} \times$ height $(cm)^{0.3964} \times 0.024265$ (Haycock et al. 1978).

2.4. Potential confounders and covariates

Children's birth anthropometrics were measured by trained field workers (Persson et al. 2012). Season of birth was defined as pre-monsoon (January–May), monsoon (June–September) and post-monsoon (October–December). At 4.5 years, children's height was measured using a stadiometer (Seca 214, Leicester Height Measure; Seca GmbH & Co., Hamburg, Germany), and weight using a digital scale (TANITA HD–318; Tanita Corporation, Tokyo, Japan). The World Health Organization (WHO) Multi-center Growth Reference Study standards were applied to convert these measures into age- and sex standardized z-scores (height for age, HAZ; weight for age, WAZ; weight for height WHZ) (de Onis et al. 2007). Maternal height and weight was measured at enrollment into the trial in early pregnancy, and BMI was calculated (kg/m^2). To assess family socioeconomic status (SES), a wealth index was generated that included data on land ownership, the construction material of the house, and ownership of different household assets (Saha et al. 2008).

2.5. Statistical analyzes

Statistical analyzes were performed using STATA (version 12, Statacorp, TX, USA). Bivariate associations between continuous variables were assessed using Spearman correlations, whereas the difference between two independent groups was assessed using Mann–Whitney *U*-test. We visually examined all evaluated associations by plotting the outcomes against the element concentrations. In the plots with U-Cd, the lowess moving-average curve indicated non-linear relationships for eGFR (Fig. 2A). The potential association between cadmium and eGFR was therefore assessed by multivariable-adjusted spline regression analyzes with knot at 0.12 μg/L (the increase up to this point is probably due to increased food intake, i.e. the beneficial effects of energy and nutrients might exceed the negative effects of increased cadmium intake), as indicated by the plot (Fig. 2A). However, we also assessed the linear relationship (without spline) to evaluate the robustness of the finding. Associations between U-Cd and blood pressure (Fig. 2C and D), and between U-As and all outcomes appeared linear, and thus, multivariable-adjusted linear regression was applied. Kidney volume and U-Cd was also assessed using multivariable-adjusted linear regression, since there were only 9 observations above the indicated "turning point" (~0.8 μg/L; Fig. 2B). We also assessed, by multivariable-adjusted linear regression, the impact of concurrent U-Se, using this as the exposure variable. The regression models were adjusted for covariates that were correlated with both exposure and outcome or known to affect kidney function; i.e. child gender, birth weight, season of birth, age at outcome measurement, WAZ, maternal BMI at GW 8, parity and SES. The spearman correlation coefficient limit for collinearity was set at 0.60. Normality plots were used to test all regression models.

Gender differences for associations between toxic metals, kidney function and blood pressure were assessed by stratifying the regression models by gender (except for kidney volume, due to small sample size, $n = 375$). In addition, we stratified the models for U-As and U-Cd on U-Se (above or below median of 12.6 μg/L; except for kidney volume) to assess whether selenium status could be an effect modifier. Also, we stratified on concurrent underweight and stunting (< -2SD of WAZ and HAZ) to assess whether these children were more susceptible to kidney or cardiovascular damage from toxic metals.

In sensitivity analyzes, we assessed the effect of U-Cd on all

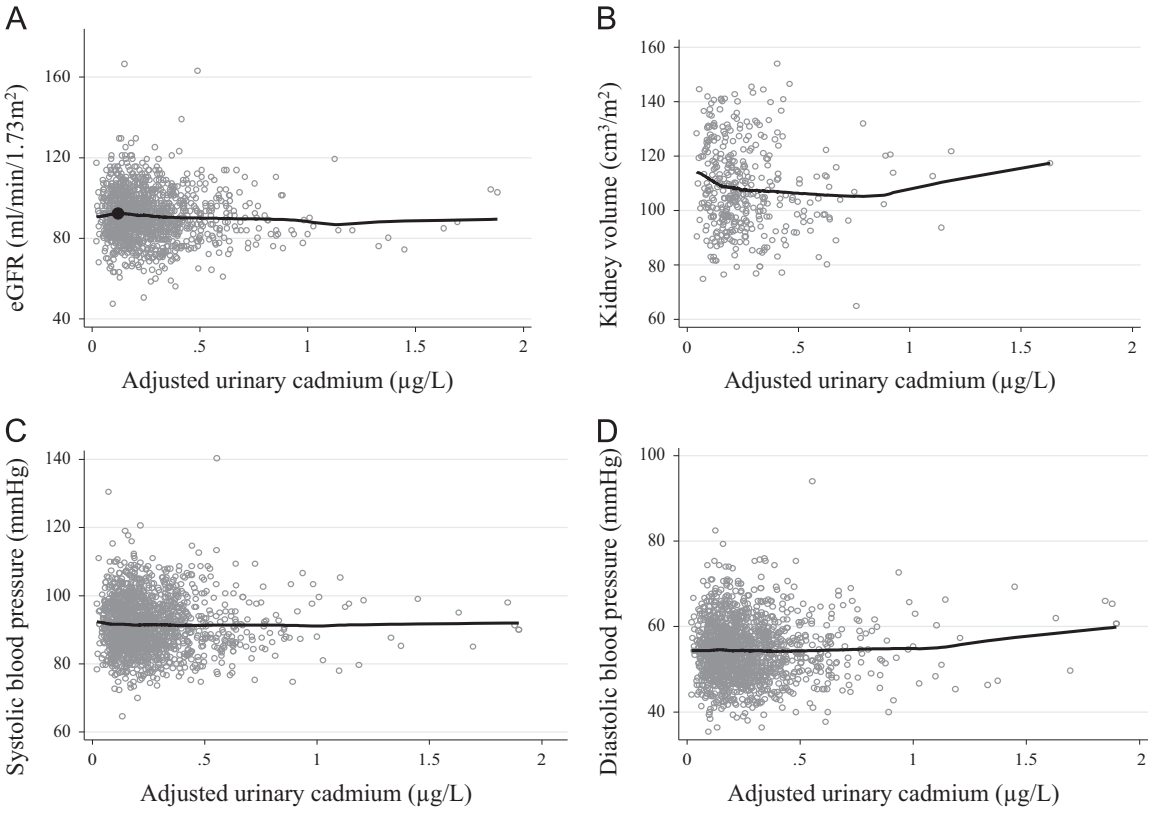

Fig. 2. Scatter plots with smoothed lowess lines for urinary cadmium (< 2.0 μg/L) and (A) eGFR, (B) kidney volume, (C) systolic blood pressure and (D) diastolic blood pressure. Black dot indicates spline knot position (0.12 for eGFR). eGFR, estimated glomerular filtration rate.

outcomes excluding observations with U-Cd above 1.0 μg/L (up to 99th percentile, $n=17$), to assess whether the top 1% in U-Cd had a large impact on the estimates. Further, we additionally adjusted all models for supplementation group, as this has been shown to have a small impact on the outcomes in our previous study (Hawkesworth et al. 2013a). In addition, we adjusted for arsenic and selenium when assessing the impact cadmium, and for cadmium and selenium when assessing associations with arsenic. Similarly, we adjusted for arsenic and cadmium when assessing associations between kidney and cardiovascular function and selenium. Finally, we adjusted the models for prenatal (maternal) urinary arsenic and cadmium, which had previously been analyzed with ICP-MS and HPLC-HG-ICP-MS as described above (Gardner et al. 2011; Kippler et al. 2012a). Because both arsenic and cadmium are known to affect birth weight (Kippler et al. 2012a; Rahman et al. 2009), a risk factor for impaired kidney function (Luyckx et al. 2013), we temporarily removed birth weight from the models in the sensitivity analyzes.

3. Results

Children with the different types of kidney or blood pressure measurements did not differ from each other (Table 1), but those with arsenic, cadmium and selenium measurements were marginally younger (4.5 vs. 4.6 years old), had mothers with slightly lower BMI (20.0 vs. 20.3 kg/m^2), had on average more siblings (parity 1.4 vs. 1.3), and belonged to families with a lower SES (−0.11 vs. 0.10), compared to those without their elements measured (p for all <0.05). Urinary concentrations of cadmium and selenium did not differ markedly between children with and without the different kidney and blood pressure measurements. Arsenic concentrations did not differ between children with and without their eGFR or blood pressure assessed, but were marginally higher among children without their kidney volumes measured (102 vs. 97 μg/L; $p=0.032$).

The studied children, 4.5 years of age, were generally lean and short (Table 1), and 39% of the children could be classified as underweight (<-2SD of WAZ; 36% of the boys, 41% of the girls), and 32% as stunted (<-2SD of HAZ; 30% of the boys, 35% of the girls). Mean birth weight of the children was 2690 g, and the prevalence of low birth weight (<2500 g) was 32%. Children's overall median U-As was 52 μg/L, with a wide range of 4–1020 μg/L. The median U-Cd was 0.22 μg/L (range 0.020-3.8 μg/L), and U-Se 12.6 μg/L (range 0.15-61.5 μg/L). Applying height and age-specific cut-offs for blood pressure (National high blood pressure education program working group on hypertension control in children and adolescents 1996), 2.4% of the girls and 1.7% of the boys were classified as hypertensive [systolic blood pressure above 108 mm Hg for boys and 107 mm Hg for girls, or diastolic blood pressure above 69 mmHg for both boys and girls (at 5 years)]. The

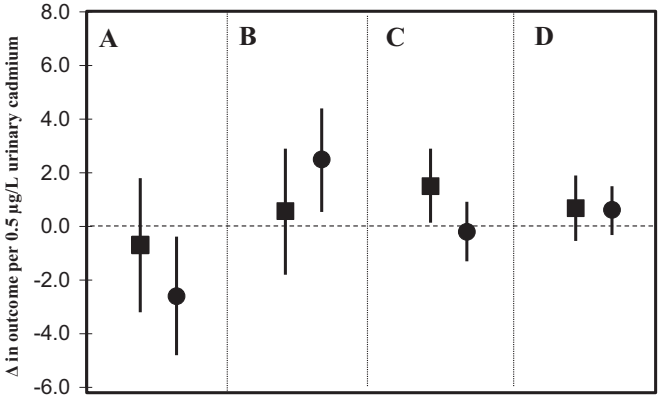

Fig. 3. Change in (A) eGFR (mL/min/1.73 m^2; above spline knot at 0.12 μg Cd/L), (B) Cystatin C (mg/L; above spline knot at 0.12 μg/L; to be divided by 100), (C) systolic blood pressure (mmHg), and (D) diastolic blood pressure (mm Hg), among boys (squares) and girls (circles) per every 0.5 μg/L increase in urinary cadmium (median=0.22 μg/L). Adjustments: sex, birth weight, season of birth, age at outcome measurement, weight for age z-score, maternal BMI at GW 8, parity and SES. To note, the positive association with systolic blood pressure in boys was mainly driven by 1 sample at 3 μg/L. Excluding this sample resulted in no significant association (B=1.1, 95% CI: −0.54, 2.7, $p=0.19$).

Table 2
Multivariable-adjusted[a] regression analysis of the association between children's exposure to arsenic, cadmium[b] and selenium, measured as concentrations in urine at 5 years of age and different markers for kidney-related outcomes.

	eGFR mL/min/1.73 m^2; $n=1106$	Cystatin C mg/L; $n=1106$	Kidney volume cm3/m^2; $n=375$	Systolic BP mm Hg; $n=1356$	Diastolic BP mm Hg; $n=1356$
U-Se					
Model 1					
B (95% CI)	0.020 (−1.0, 1.1)	0.0016 (−0.0081, 0.011)	−1.6 (−4.4, 1.1)	0.081 (−0.54, 0.70)	0.27 (−0.27, 0.80)
p-value	0.97	0.74	0.24	0.80	0.33
Model 2					
B (95% CI)	0.34 (−0.76, 1.4)	−0.0013 (−0.011, 0.0087)	−1.3 (−4.2, 1.5)	0.038 (−0.60, 0.68)	0.18 (−0.37, 0.73)
p-value	0.55	0.80	0.35	0.91	0.52
U-As					
Model 1					
B (95% CI)	−0.30 (−0.86, 0.26)	0.0031 (−0.0020, 0.0083)	−0.47 (−2.0, 1.0)	−0.17 (−0.51, 0.17)	−0.0063 (−0.30, 0.28)
p-value	0.30	0.23	0.54	0.33	0.97
Model 2					
B (95% CI)	−0.29 (−0.86, 0.28)	0.0029 (−0.0022, 0.0081)	−0.47 (−2.0, 1.0)	−0.18 (−0.52, 0.16)	−0.026 (−0.32, 0.26)
p-value	0.32	0.27	0.55	0.30	0.86
U-Cd[b]					
Model 1					
B (95% CI)	−1.7 (−3.4, −0.051)	0.016 (0.00070, 0.031)	−1.9(−5.0, 1.1)	0.48 (−0.39, 1.4)	0.65 (−0.095, 1.4)
p-value	0.043	0.040	0.20	0.28	0.087
Model 2					
B (95% CI)	−1.8 (−3.4, −0.071)	0.016 (0.00036, 0.031)	−1.6 (−4.7, 1.6)	0.49 (−0.40, 1.4)	0.60 (−0.16, 1.4)
p-value	0.041	0.045	0.32	0.28	0.12

BP, blood pressure; eGFR, Estimated glomerular filtration rate; U-As, urinary arsenic; U-Cd, urinary cadmium; U-Se, urinary selenium.

[a] Model 1: Adjusted for sex, birth weight, season of birth, age at outcome measurement, weight for age z-score, maternal BMI at GW 8, parity and SES. Model 2: Further adjusted for arsenic, cadmium and selenium. B-value for urinary arsenic is expressed per 100 μg/L, for cadmium per 0.5 μg/L (above the spline knot at 0.12 μg/L for eGFR and Cystatin C) and for selenium per 10 μg/L.

[b] For association between U-Cd, eGFR and cystatin C, multivariable-adjusted spline regression have been used (knot at 0.12 μg/L).

mean eGFR was 92 ml/min/1.73 m^2 (Hoek equation), with slightly higher values in girls than in boys (93 vs. 90 mL/min/1.73 m^2, $p=0.0023$). There was no difference in kidney volume between boys and girls (107.8 vs. 109.2 cm^3/m^2, $p=0.67$).

We found a weak positive correlation between children's U-As and U-Cd levels ($r_s=0.11$; $p<0.001$), as well as between U-Se and U-Cd ($r_s=0.23$; $p<0.001$), and between U-Se and U-As ($r_s=0.062$; $p=0.021$).

In the multivariable-adjusted linear regression analysis, we found no associations between the children's arsenic exposure and any of the studied outcomes (Table 2). Regarding the cadmium exposure, the adjusted spline regression models showed an inverse association between children's U-Cd and eGFR above the spline knot of 0.12 μg/L (Table 2). There was no significant association below the spline knot for eGFR (B=3.3; 95% CI: −21, 28; $p=0.79$; $n=181$). The association between eGFR and U-Cd was apparent also when using linear regression instead of spline (B=−1.6; 95% CI: −3.2, −0.029; $p=0.046$). Stratifying the spline regression analyzes on gender revealed that the association between U-Cd and eGFR was apparent mainly among girls (B=−2.6; 95% CI: −4.8, −0.37; $p=0.022$; boys: B=−0.69; 95% CI: −3.2, 1.8; $p=0.59$; Fig. 3). As for all children, the association was also evident when using linear regression (girls: B=−2.1; 95% CI: −4−1, −0.18; $p=0.032$; boys: B=−0.83; 95% CI: −3.2, 1.6; $p=0.50$), although the girls' estimate decreased somewhat. We tested the potential impact of a few very high U-Cd concentrations (17 children) by restricting the regression models with all children to observations within the 99th percentile of U-Cd concentrations (below 1.0 μg/L). This increased the negative estimates for eGFR quite markedly in all children [B from −1.7 (95% CI: −3.4,−0.051; $p=0.043$) to−2.9 (95% CI: −5.3, −0.48; $p=0.019$)], and in the girls [B from −2.6; (95% CI: −4.8, −0.37; $p=0.022$) to −3.8; (95% CI: −7.1, −0.60; $p=0.020$)]. Effects of U-Cd were also evident when using cystatin C as a marker for kidney function (Table 2). As with the eGFR, the association with cystatin C was mainly seen in girls (Fig. 3), and exclusion of the top 1% U-Cd values showed higher estimates for U-Cd above the spline knot (all children: B=0.035; 95% CI=0.0065, 0.063; $p=0.016$).

There was also an inverse association between U-Cd and kidney volume, although not statistically significant (Table 2). Assessing the association between U-Cd and kidney volume after excluding the few, very high observations (above 1.0 μg/L; $n=5$; Fig. 2) showed that this had a high impact on the estimate for U-Cd (B from−2.0 (95% CI: −5.0, −1.1; $p=0.20$) to −4.2 (95% CI: −9.2, 0.91; $p=0.11$; $n=370$). We did not further stratify on gender due to the small sample size.

We found no association between U-Cd and blood pressure in all children, and excluding the top 1% data did not reveal any clear associations either. Upon stratification by gender, a positive association with systolic blood pressure was evident among boys (Fig. 3). However, after excluding the highest U-Cd observation among the boys with their blood pressure measured (1 sample at 3.0 μg/L) this association was no longer significant (B=1.1, 95% CI: −0.54, 2.7, $p=0.19$)

When assessing the effect of selenium alone, we found no associations with any of the outcomes, either before or after further adjusting for U-As and U-Cd (Table 2). Stratifying the models with all children on U-Se (above or below median of 12.6 μg/L), however, revealed a three times stronger inverse association between cadmium and eGFR in the stratum with low U-Se, compared to those with high U-Se (Fig. 4), even though the low selenium group also had lower U-Cd median: 0.19 μg/L vs. 0.24 μg/L in high Se group ($p<0.001$). The stratification on selenium did not result in any clear differences regarding the effect of U-Cd on blood pressure (Fig. 4). We did not additionally stratify the analyzes on gender due to low power.

In sensitivity analyzes, we further adjusted all the above statistical models for the different prenatal supplementation arms (six groups), which did not have any impact on any of the estimates (data not shown). We also additionally adjusted for U-As and U-Se when assessing the associations with cadmium, and for U-Cd and U-Se when assessing the associations with arsenic, which had marginal influence on the estimates (Table 2). Adjusting for prenatal U-Cd and U-As at GW8 did not influence the estimates for concurrent U-Cd either (data not shown). Temporarily removing birth weight from the models did not change the estimates for cadmium, arsenic or selenium in relation to any of the outcomes (data not shown). Stratifying the analyzes for all children on concurrent underweight (< −2 SD of WAZ) and stunting (< −2SD of HAZ) revealed no clear differences either (data not shown).

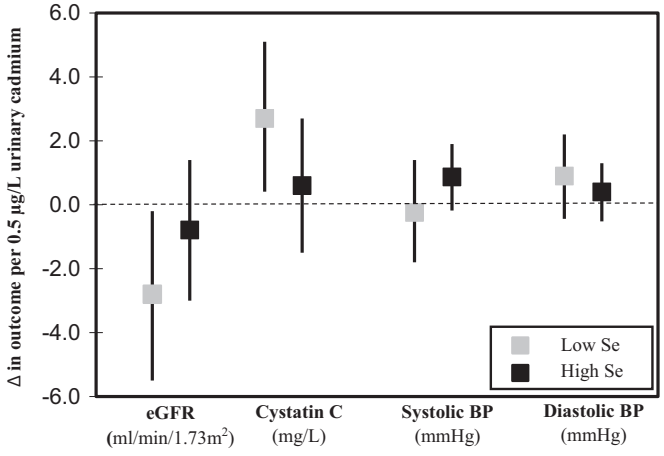

Fig. 4. Multivariable-adjusted linear regression coefficient and 95% CI for each outcome in relation to children's urinary cadmium (per 0.5 μg/L, median=0.22 μg/L; above spline knot at 0.12 for eGFR and cystatin C), stratified by high and low selenium (categorized as above and below the median; < and > 12.6 μg/L). The regression models are adjusted for sex, birth weight, season of birth, age at outcome measurement, weight for age z-score, maternal BMI at GW 8, parity and SES.

4. Discussion

This cohort study of rural Bangladeshi preschool-aged children indicates that chronic exposure to cadmium may impair kidney function, particularly in girls. In these, an increase of 0.5 μg/L in urinary cadmium (overall median 0.22 μg/L) was associated with a decrease in eGFR by on average 0.2SD ($p=0.022$). The suggested inverse association also with kidney volume further supports a nephrotoxic effect of dietary cadmium in the children. Stratifying on concurrent urinary selenium revealed that the inverse association between childhood cadmium and eGFR was about three times stronger in the stratum with low selenium (below median of 12.6 μg/L), compared to the stratum with higher selenium status, indicating a protective effect of adequate selenium status.

We found effects mainly related to the eGFR, while the previous European study (de Burbure et al. 2006) showed that children's urinary cadmium was mainly associated with impaired renal tubular function (assessed by urinary retinol-binding protein, Clara cell protein 16, and N-acetyl-beta-D-glucosaminidase), not serum cystatin C or creatinine. However, the indicated blood lead-associated renal hyper filtration in that study could have masked an adverse effect of cadmium. Also, the children were older (mean 10 years). Unfortunately, no markers of tubular function were available in the present study.

The observed stronger associations between kidney function and childhood exposure to cadmium than to arsenic are in line

with the fact that cadmium accumulates in the kidneys and is known to be a potent nephrotoxicant also at low-level exposure in numerous studies on adults (Jarup and Akesson 2009). Furthermore, cadmium is a more effective inducer of oxidative stress than arsenic in both children (Kippler et al. 2011) and adults (Engstrom et al. 2010). Oxidative stress is indeed a proposed mechanism of impaired kidney development (Thompson and Al-Hasan 2012), and this mechanism of cadmium-related nephrotoxicity is supported by our observed strengthening of the inverse associations between cadmium on eGFR when restricting the analysis to the children with low concentrations of selenium (below median), a well-documented antioxidant (Roman et al. 2014). Interestingly, this was the case even though the concentrations of U-Cd were lower in this group (median: 0.19 and 0.24 μg/L in the low and high selenium groups, respectively, $p<0.001$). Protective effects of selenium against cadmium-induced oxidative stress and nephrotoxicity have previously been shown in mice and rats (Wang et al. 2013; Xiao et al. 2002). It is unlikely that U-Se reflected nutritional status in general as U-Se was only weakly correlated with WAZ ($r_s=0.11$, $p<0.001$) and SES ($r_s=0.20$, $p<0.001$), which would support a true protective effect of selenium. We previously found that the average selenium concentration in rice samples retrieved from 66 of the families in the present cohort contained on average 48 μg selenium/kg dry weight, leading to an approximate daily intake between 17–36 μg/day for women in the study area, i.e. 25–50% of the recommended daily intake (Gardner et al. 2011; Skröder et al., 2014). Thus, we believe that this is the main source of selenium intake in the present population, although a small part might also come from minor dietary components, such as fish and vegetables.

The reasons for the observed gender differences are not known, as boys and girls had no difference in U-Cd concentrations (median 0.21 vs. 0.22 μg/L, respectively). The gender related differences may be related to the endocrine disrupting properties of cadmium, particularly interactions with growth, thyroid and sex hormones (Iijima et al. 2007; Johnson et al. 2003; Turgut et al. 2005). We have previously found stronger adverse effects of cadmium on growth and cognitive function in girls, compared to boys in the same cohort (Gardner et al. 2013; Kippler et al. 2012b). Also, the epigenetic effects of cadmium (DNA methylation in cord blood) showed marked sex differences (Kippler et al. 2013). In the newborn girls, cadmium was mainly associated with methylation changes in genes associated with organ development, morphology and mineralization of bone, whereas the changes in boys were mainly in cell death-related genes. Obviously, the mechanisms behind the observed gender differences in the adverse effects of cadmium in childhood need to be investigated further.

The adverse effects of cadmium in these preschool-aged children are of concern as the exposure is mainly through rice (Kippler et al. 2010), the main staple food for about 3.5 billion people globally, including Bangladesh (Muthayya et al. 2014). The rural Matlab study area had essentially no industrial or vehicle-derived pollution. Most plants, but rice in particular, are known to take up cadmium from the soil, and this is reflected in elevated exposure levels in people on vegetarian diets globally (Berglund et al. 1994; Meharg et al. 2013). Children are at particular risk of elevated body burden as exposure through rice-based food starts very early in life, when the energy intake per kg body weight is high, and the gastrointestinal absorption might be higher than later in life (Kippler et al. 2010). The half-life of kidney cadmium is extremely long, about 45 years according to recent estimations (Fransson et al. 2014), leading to a constant increase in kidney cadmium with age. Indeed, somewhat higher urinary concentrations (median 0.36 μg/L) than in the present study was found in children at 6–12 years of age in a parallel cohort in the same study area (Berglund et al. 2011). Even higher urinary cadmium concentrations have been reported for preschool-aged children in Japan and other Asian countries (Watanabe et al. 2013). For comparison, an average urine cadmium concentration of <0.1 μg/L was reported for children of similar age in the NHANES cohort in USA (Riederer et al. 2013), as well as in Europe (Pirard et al. 2014; Schulz et al. 2009); most likely related to a lower consumption of cadmium via food.

The modest effects of arsenic, if any, on kidney function, even in children with high arsenic exposure (>123 μg/L, 75th percentile), are reassuring from a public health perspective. However, inverse effects on kidney function due to arsenic exposure have previously been shown in Bangladeshi adults (Peters et al. 2014). Thus, it is likely that arsenic is indeed nephrotoxic, although the symptoms manifest later in life. In Bangladesh, as well as many other areas of the world, millions of children are exposed to arsenic through drinking water (Gardner et al. 2011) and rice-based food (Davis et al. 2012; Ljung et al. 2011). There are also other severe health effects of arsenic such as impaired cognitive development (Hamadani et al. 2011) and various forms of cancer, the risk of which seems to increase markedly after exposure early in life (Smith et al. 2012).

The main strengths of this study include the large sample size, with wide variation in metals exposure assessed by individual biomarkers, measured by ICP-MS. Also, we assessed kidney function based on plasma cystatin C-derived eGFR and kidney volume, and used the Hoek equation to estimate the GFR, which was recently found to be a suitable equation for children (Zachwieja et al. 2014). In our previous studies, we used the Grubb equation, which gave much higher eGFR values, in line with other recent studies (Gheissari et al. 2014), while the eGFR obtained with the Hoek equation (mean 92 mL/min/1.73 m^2) was slightly lower than that found in other studies of this age group (114 ± 19 mL/min/1.73 m^2) (Schwartz and Work 2009). However, the correlation between the two equations was very strong ($r_s=0.99$, $p<0.001$), and the association with U-Cd was found to be similar regardless of equation. A limitation of this study was the inability to evaluate the effect on renal tubular function, and the low number of children with kidney volume measurements who also had arsenic, cadmium and selenium measured. Also, we had no data on blood selenium concentrations, which is generally used as a biomarker of selenium status. The protective effects are thus to be interpreted with caution, but might as well have been underestimated. It is also unfortunate that the outcomes were measured slightly before the exposure; however, both arsenic and cadmium exposure has been shown to be quite persistent over time in the present population (Gardner et al. 2011; Kippler et al. 2007). If anything, a potential exposure misclassification is likely to have biased toward the null value.

5. Conclusions

The study indicates adverse effects of childhood cadmium exposure on kidney function. However, it is important to follow up these children to assess potential long-term consequences of the findings. Considering the millions of children with prevalent exposure to multiple nephrotoxic environmental pollutants, it is important to limit environmental contamination by cadmium as much as possible.

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