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# Environmental metal exposure and growth to 10 years of age in a longitudinal mother–child cohort in rural Bangladesh

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ABSTRACT

*Background:* Early-life exposure to arsenic (As), cadmium (Cd), and lead (Pb) has been linked to smaller birth and early childhood anthropometry, but little is known beyond the first years in life.
*Objectives:* To evaluate the impact of gestational and childhood exposures to As, Cd, and Pb on growth up to 10 years of age.
*Methods:* We studied 1530 mother–child dyads from a nested sub-cohort of the MINIMat trial in rural Matlab, Bangladesh. Metal concentrations in maternal erythrocytes during pregnancy and in children's urine at 10y were measured by inductively coupled plasma mass spectroscopy. Child height and weight were measured at 19 occasions from birth until 10y and converted to height-for-age Z-scores (HAZ) and weight-for-age Z-scores (WAZ). Associations between $\log_2$-transformed metal concentrations and growth parameters were assessed with multivariable-adjusted regression models.
*Results:* Children's concurrent urinary Cd (median 0.24 μg/L), reflecting long-term exposure, was inversely associated with WAZ (B: −0.072; 95% confidence interval (CI): −0.12, −0.020; p = 0.007), and possibly HAZ (B: −0.046; 95% CI: −0.096, 0.0014; p = 0.057), at 10y. The association with WAZ was stronger in boys than in girls. Maternal erythrocyte Cd (median 0.90 μg/kg) during pregnancy was inversely associated with WAZ during childhood only in boys (B: −0.071, 95% CI: −0.14, −0.0047, p = 0.036). Concurrent urinary Pb (median 1.6 μg/L) was inversely associated with WAZ (B: −0.084; 95% CI: −0.16, −0.0085; p = 0.029) and HAZ (B: −0.087; 95% CI: −0.15, −0.021; p = 0.010) in boys, but not in girls. Neither gestational nor childhood As exposure (median maternal erythrocyte As 4.3 μg/kg and children's urinary As 57 μg/L) was associated with growth up to 10y.
*Conclusions:* While all effect estimates were small, environmental exposure to Cd and Pb is common and impaired growth is of public health concern, especially for children already at risk of reduced growth due to malnutrition. Gender differences in susceptibility need further investigation.

## 1. Introduction

Child growth and development are influenced by multiple factors, including nutritional status, socio-economic conditions, genetics, and exposure to toxic chemicals (Bellinger 2012; Black et al. 2013). Among the top ten chemicals of major public health concern, the World Health Organization (WHO) lists the toxic metals arsenic (As), cadmium (Cd), and lead (Pb) (WHO, n.d.). Children are exposed to these metals primarily through food and drinking water, and Pb exposure may also occur via dust, soil, toys, and household products (Brammer and Ravenscroft 2009; EFSA 2009; 2013). Early-life exposure to toxic metals may impair outcomes such as neurodevelopment (Gustin et al. 2018; Kippler et al. 2012b; Kippler et al. 2016a; Sanders et al. 2015; Vahter et al. 2020), immune function (Ahmed et al. 2014), and bone health (Malin Igra et al. 2019; Sughis et al. 2011).

Lately, emerging evidence also suggests that early-life metal

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exposure can affect growth. Several large observational studies have reported an inverse association between gestational exposure to Cd and size at birth, especially in newborn girls (Kippler et al. 2012a; Rollin et al. 2015; Taylor et al. 2016), as well as decreased weight, height and/or head circumference up to 4 years of age (Chatzi et al. 2018; Lin et al. 2011). Studies of gestational exposure to As and Pb on size at birth and early childhood growth report inconsistent results (Muse et al. 2020; Rahman et al. 2017; Signes-Pastor et al. 2019; Zheng et al. 2016; Zhong et al. 2019). A few studies have also found As, Cd or Pb exposure during childhood to be associated with children's weight and height (Ballew et al. 1999; Burns et al. 2017; Gardner et al. 2013; Saha et al. 2012; Zhou et al. 2020). Some of the As- and Cd-related associations were more pronounced in girls (Gardner et al. 2013; Saha et al. 2012), while the associations with Pb were more pronounced in boys (Zhou et al. 2020).

Apart from one study involving Pb exposure in boys who were annually assessed from 8 to 18 years of age (Burns et al. 2017), longitudinal studies of early-life toxic metal exposure and children's growth beyond the first few years of life are lacking. Therefore, we aim to investigate if the previously observed metal-related associations with anthropometry among Bangladeshi children from birth up to 5 years of age (Gardner et al. 2013; Kippler et al. 2012a; Kippler et al. 2012c; Rahman et al. 2009; Saha et al. 2012) still persist at 10 years of age, and if the associations differ between boys and girls.

## 2. Materials and methods

### 2.1. Study population

The present study was conducted in a mother–child cohort in Matlab, a non-industrialized rural area, about 50 km south-east of Dhaka in Bangladesh. The cohort was established to investigate the health effects of exposure to several toxic agents early in life. The studied toxicants include As, which is a known contaminant of tube well water and rice (Kippler et al. 2016b; Vahter et al. 2006), Cd originating from rice and other plant-based foods (Kippler et al. 2012a), and Pb, which may also be found in rice as well as spices, cooking pots and housing materials (Bergkvist et al. 2010; Forsyth et al. 2019). Initially, the mothers were recruited to a food and micronutrient supplementation trial called MINIMat (Maternal and Infant Nutrition Interventions, Matlab) (Persson et al. 2012), which enrolled 4436 women in early pregnancy from November 2001 throughout October 2003. There were 3625 live births in the MINIMat trial. The aim of the trial was to evaluate if a combination of micronutrient and food supplementation would improve pregnancy outcomes such as maternal hemoglobin levels, size at birth and infant and child mortality (Persson et al. 2012). Briefly, the trial included six intervention groups, with three different micronutrient supplementations (30 mg iron and 400 μg folate, or 60 mg iron and 400 μg folate, or supplementation with 15 recommended micronutrients including 30 mg iron and 400 μg folate), and either early [around gestational week (GW) 9] or usual timing of food supplementation (around GW20) (Persson et al. 2012).

This study included 1530 children, born as single babies from October 2002 throughout November 2003, who participated in the developmental follow-ups at 5 and 10 years of age (Gustin et al. 2018; Skroder et al. 2017). The participation rate was 95% at the 10-year follow-up, as 1607 children were initially invited, and the main reasons for non-participation were out-migration and parents' refusal. The children's weight and height were measured at birth and every month during the first year of life, every third month during the second year (Saha et al. 2012), and then at 5 and 10 years of age. Metal exposure biomarkers were measured during the mothers' early pregnancy and in the children at 10 years. Of the 1530 children in this study, 1523 had exposure data at 10 years of age and were included in the cross-sectional analyses, and 1439 children had data on their mothers' erythrocyte metal concentrations during pregnancy and were included in the longitudinal analyses.

The study was conducted in concordance with the Helsinki Declaration, and it has been approved by the ethical review committees at icddr, b, Dhaka, Bangladesh, and by the Regional Ethical Review Board, Stockholm, Sweden. Informed written consent was obtained from the mothers at enrollment and at later follow-ups from the children's guardians.

### 2.2. Exposure assessment

The exposure to As, Cd and Pb was assessed by concentrations in blood (erythrocyte fraction) from the mothers in early pregnancy (GW14) and in urine from the children at 10 years of age. Details of the collection of blood samples and spot urine samples have been described before (Gustin et al. 2018; Kippler et al. 2009; Skroder et al. 2017). In short, both blood and spot urine collection were conducted at the heath care facilities in Matlab. Erythrocytes and plasma were separated by centrifugation within a couple of hours. Arsenic exposure in urine was measured as total arsenic and was not speciated into the different metabolites for all children, as we have previously found good agreement between the two methods in this population, both in the mothers (Gardner et al. 2011) and in a sub-sample of the children at 9 years of age (Skröder Löveborn et al. 2016). As and Pb are readily excreted in urine within a few days of exposure, and thus, their concentrations in urine (U-As and U-Pb) are short-term exposure biomarkers (Bergkvist et al. 2010; Vahter 2002). Cadmium concentrations in urine (U-Cd) are, on the other hand, a measure of long-term exposure as Cd accumulates in the renal cortex with a half-life of decades (Akerstrom et al. 2013). Metal concentrations in erythrocytes (Ery-As, Ery-Cd and Ery-Pb) reflect the exposure of the last few months, as the erythrocytes' lifespan is about 3–4 months (Neve 1995). The metal concentration in blood is also the fraction that can be transferred to the fetus (As and Pb) (Chen et al. 2014; Concha et al. 1998) or be accumulated in placenta (Cd) (Osman et al. 2000). Therefore, blood concentrations were chosen to reflect exposure during pregnancy. Unfortunately, a blood sample was not collected from the children.

The concentrations of As ($m/z$ 75), Cd ($m/z$ 111), and Pb ($m/z$ 208) were measured using inductively coupled plasma mass spectrometry [(ICPMS), Agilent 7500ce or 7700ce, Agilent Technologies, Japan] at our laboratory at Karolinska Institutet, Stockholm, Sweden. Before analysis, urine samples were diluted 1:10 with 1% nitric acid (Scharlau, Scharlab, Sentmenat, Spain or Ultrapure Normatom; VWR Chemicals). The erythrocyte samples were diluted 1:25 in an alkali solution [2% (wt:vol) 1-butanol, 0.05% (wt:vol) EDTA, 0.05% (wt:vol) Triton X-100, 1% (wt:vol) ammonium hydroxide ($NH_4OH$) and 20 μg/L internal standard; Sigma-Aldrich], and then they were vortex mixed, sonicated for 5 min, and centrifuged at 179 × g for 2 min [MSE centrifuge, Super Minor; MSE (UK) Ltd.]. Supplementary Table S1 summarizes the results of the quality control samples and the limit of detection (LOD) of the different metal exposure biomarkers. No samples were found to have metal concentrations below the LOD. A minor fraction of the maternal erythrocyte samples (n = 426) was analyzed using acid digestion prior to the ICPMS analyses (Kippler et al. 2009), instead of the alkali dilution described above. The two methods gave strongly correlated results (Lu et al. 2015). However, the As, Cd and Pb concentrations were found to be consistently 5%, 9% and 10% lower following the alkali method, respectively. Therefore, the concentrations of As obtained with the acidic method were multiplied by 0.95, Cd by 0.91, and Pb by 0.90. Metal concentrations in urine were adjusted for specific gravity (mean 1.012 in the children), which was measured with a refractometer (EUROMEX RD712 Clinical Refractometer, EUROMEX Holland, Anhem, The Netherlands), to compensate for variation in urine dilution (Nermell et al. 2008).

### 2.3. Outcomes

Height-for-age and weight-for-age Z-scores (HAZ and WAZ) were

calculated from the measured height and weight through the child growth international reference values developed by the WHO (de Onis et al. 2007; WHO 2006). Child height/length and weight were measured by trained nurses at birth, every month of the first year of the child's life, every third month of the second year and at 5 and 10 years of age, resulting in a total of 19 measurements. The children were weighed with a daily calibrated digital scale (TANITA HD-318; Tanita Corporation). Until 1.5 years of age, length was measured with a collapsible length board with a precision of 0.1 cm. At later ages, height was measured with a regularly calibrated free-standing stadiometer Leicester Height Measure (Seca214). Stunting and underweight were defined as having a HAZ and WAZ below −2, respectively, while overweight was classified as having WAZ between 1 and 2, and obesity as WAZ over 2.

### 2.4. Covariates

The families' socioeconomic status (SES) was estimated via a wealth score at enrollment and at the 10-year follow-up. The score was categorized into quintiles and it is based on information regarding type of housing structure, dwelling characteristics and family ownership of assets (Gwatkin et al. 2000). Maternal weight (kg) and height (cm) were measured at enrollment (around GW8) with an electronic scale (Uniscale; SECA) with a precision of 0.1 kg and a stadiometer to the nearest 0.1 cm, respectively. Maternal education (number of years of formal schooling) and parity (number of living children) were enquired at enrollment and at 10 years. Season of conception was categorized as pre-monsoon (March-May), monsoon (June-October), or post-monsoon (November-February). The age of the child at the 10-year follow-up was used as a continuous variable in the cross-sectional analyses (in years), while it was used as a splined variable with five knots in the longitudinal analyses (in months).

### 2.5. Statistical analyses

All statistical analyses were performed with Stata (version 16, StataCorp) and a p-value below 0.05 was considered statistically significant. However, we also evaluated consistency of data. Spearman's rank correlation was used to assess bivariate correlations between continuous variables. Mann-Whitney *U* test and Pearson's chi-square test were used to test differences between boys and girls in continuous and categorical variables, respectively. As we have previously reported gender-related associations of early-life metal exposure and child anthropometry (Gardner et al. 2013; Kippler et al. 2012a; Malin Igra et al. 2019), all modelling was initially conducted using all children, and thereafter, stratified by child gender. Associations of metal exposure biomarkers with child anthropometry measures were visualized using scatter plots

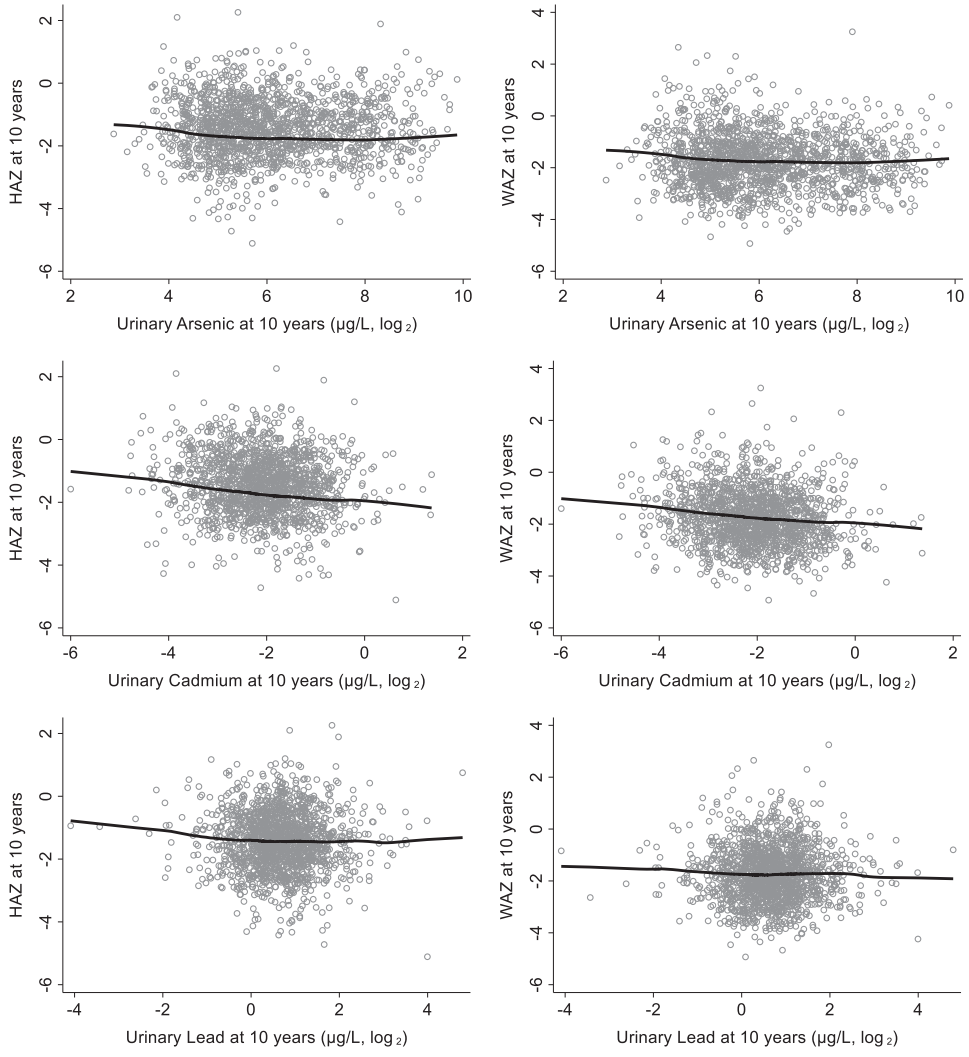


**Fig. 1.** Scatter plots with lowess lines of urinary metal concentrations (arsenic, cadmium, and lead; $log_2$-transformed) at 10 years and height-for-age Z-scores (HAZ) and weight-for-age Z-scores (WAZ) at 10 years.

with Lowess smoothing lines.

Cross-sectional analyses of associations between urinary metal concentrations (U-As, U-Cd and U-Pb) and anthropometry (HAZ and WAZ) at 10 years of age were conducted using linear regression, since scatter plots with Lowess smoothing lines indicated that linearity could be assumed (Fig. 1). As the metal concentrations had a right-skewed distribution, all exposure biomarkers were $\log_2$-transformed. Model 1 presents the crude unadjusted associations between the urinary metal concentrations and the anthropometry outcomes. Model 2 was adjusted for child gender, age of the child, maternal education, parity, and family SES at 10 years of age, and maternal height in models with HAZ and maternal weight at GW8 in models with WAZ. Maternal height, maternal education and season of conception have previously been identified as predictors of stunting at 10 years of age in the MINIMat cohort (Svefors et al. 2016).

Subsequently, we used linear regression analyses to investigate if there were any associations between maternal erythrocyte metal concentrations during early pregnancy (Ery-As, Ery-Cd and Ery-Pb at GW14) with HAZ and WAZ at 10 years. As for the cross-sectional analyses, Model 1 represents crude unadjusted associations. Model 2 was adjusted for child gender, age of the child at 10 years, season of conception, maternal education, parity, family SES at enrollment, and maternal height in relation to HAZ. The latter was exchanged to maternal weight at GW8 in relation to WAZ.

Lastly, we performed longitudinal analyses of associations of maternal erythrocyte metal concentrations during early pregnancy (Ery-As, Ery-Cd and Ery-Pb at GW14) with growth from birth to 10 years of age (19 measurement of HAZ and WAZ) using multivariate linear regression. A robust, clustered variance–covariance matrix estimator used each individual as a separate cluster, adjusting for the intra-person correlation. As above, Model 1 represents crude unadjusted associations. Model 2 was adjusted for child gender, age of the child in months (five spline knots at ages 2, 6, 12, 24, and 52 months), season of conception, maternal education, parity, family SES at enrollment, and maternal height (used in relation to HAZ) or weight at GW8 (used in relation to WAZ). Time was modelled as a splined variable with five knots as it was theoretically preferable, and it provided a better model fit judging by the statistical significance of the beta coefficient as well as both AIC (Akaike Information Criterion) and BIC (Bayesian Information Criterion).

We checked for acceptable normal distribution of the residuals in all the models with q-q plots and residual versus fitted plots. For the sake of easier interpretation of our results, when we encountered statistical significance in the analyses described above, we constructed models with height and weight as outcome instead of HAZ and WAZ (Spearman's correlation between both height and HAZ and weight and WAZ $r_S = 0.99$, $p < 0.001$) adjusted as Model 2 and compared the highest tertile of exposure with the lowest tertile.

As sensitivity analysis, all models described above were constructed with mutually adjusted metals, including all three metals at the same time point simultaneously (Model 3). Although the intervention group was reported not to be associated with child growth in an earlier study (Svefors et al. 2016), we also adjusted for the MINIMat nutritional intervention groups in pregnancy (6 categories, Model 4).

**Table 1**
Characteristics and exposure biomarkers of all the children and their mothers, and stratified by child gender.

| | All children | | Boys | | Girls | | |
|---|---|---|---|---|---|---|---|
| | n | Median (5th-95th percentile) or Mean ± SD | n | Median (5th-95th percentile) or Mean ± SD | n | Median (5th-95th percentile) or Mean ± SD | p-value[a] |
| **Characteristics** | | | | | | | |
| Child age (years)[b] | 1530 | 9.5 (9.4; 9.7) | 803 | 9.5 (9.4; 9.7) | 727 | 9.5 (9.4; 9.7) | 0.67 |
| Child weight (kg)[b] | 1530 | 22.8 (18.4; 30.0) | 803 | 23.0 (18.8; 30.0) | 727 | 22.5 (18.1; 30.0) | 0.005 |
| Child height (cm)[b] | 1530 | 127 (118; 136) | 803 | 127 (118; 137) | 727 | 126 (117; 136) | 0.62 |
| Child WAZ[b] | 1529 | −1.7 ± 1.0 | 802 | −1.7 ± 1.0 | 727 | −1.8 ± 1.0 | 0.10 |
| Child HAZ[b] | 1530 | −1.4 ± 0.94 | 803 | −1.4 ± 0.93 | 727 | −1.5 ± 0.95 | 0.15 |
| SES (quintiles) %[b] | 1530 | 20/20/20/20 | 803 | 19/20/21/20/19 | 727 | 21/20/18/20/20 | 0.70 |
| Maternal education (years)[b] | 1530 | 5 (0; 10) | 802 | 5 (0; 10) | 727 | 5 (0; 10) | 0.53 |
| Parity (no. of children)[b] | 1530 | 3 (2; 5) | 803 | 3 (2; 5) | 727 | 3 (2; 5) | 0.032 |
| Birth weight (kg) | 1444 | 2.7 (2.1; 3.3) | 754 | 2.7 (2.1; 3.4) | 690 | 2.6 (2.1; 3.3) | <0.001 |
| Season of conception (3 cat.) %[c] | 1530 | 27/30/43 | 803 | 25/32/43 | 727 | 28/29/43 | 0.37 |
| Maternal age (years), enrollment | 1530 | 26 (18; 37) | 803 | 26 (18; 37) | 727 | 26 (18; 37) | 0.47 |
| Maternal height (cm) | 1530 | 150 (141; 158) | 803 | 150 (141; 158) | 727 | 150 (142; 158) | 0.92 |
| Maternal weight at GW8 (kg) | 1528 | 44 (36; 57) | 802 | 44 (36; 58) | 726 | 44 (36; 56) | 0.77 |
| SES (quintiles) %, enrollment | 1530 | 21/23/20/18/18 | 803 | 21/23/20/21/16 | 727 | 21/24/21/16/19 | 0.12 |
| Maternal education (years), enrollment | 1529 | 5 (0; 10) | 802 | 5 (0; 10) | 727 | 5 (0; 10) | 0.39 |
| Parity (no. of children), enrollment | 1530 | 1 (0; 4) | 803 | 1 (0; 4) | 727 | 1 (0; 4) | 0.58 |
| Gestational age at GW14 sampling | 1530 | 14.4 (11.6; 17.3) | 803 | 14.3 (11.4; 17.3) | 727 | 14.6 (11.6; 17.3) | 0.13 |
| **Exposure** | | | | | | | |
| U-As 10y (μg/L)[d] | 1523 | 57 (19; 375) | 800 | 60 (19; 338) | 723 | 54 (19; 395) | 0.54 |
| U-Cd 10y (μg/L)[d] | 1523 | 0.24 (0.083; 0.64) | 800 | 0.23 (0.081; 0.61) | 723 | 0.25 (0.084; 0.69) | 0.091 |
| U-Pb 10y (μg/L)[d] | 1523 | 1.6 (0.65; 4.1) | 800 | 1.5 (0.62; 4.1) | 723 | 1.6 (0.70; 4.1) | 0.25 |
| Ery-As GW14 (μg/kg) | 1439 | 4.3 (1.1; 23) | 756 | 4.1 (1.2; 24) | 683 | 4.5 (1.1; 22) | 0.67 |
| Ery-Cd GW14 (μg/kg) | 1439 | 0.90 (0.26; 2.3) | 756 | 0.93 (0.28; 2.4) | 683 | 0.87 (0.26; 2.2) | 0.063 |
| Ery-Pb GW14 (μg/kg) | 1439 | 70 (22; 153) | 756 | 68 (22; 155) | 683 | 71 (21; 150) | 0.40 |

Abbreviations: WAZ: Weight-for-age Z-score; HAZ: Height-for-age Z-score; GW: Gestational Week; SES: socioeconomic status (quintiles).
U-Cd: Urinary cadmium; U-As: Urinary arsenic; U-Pb: Urinary lead; Ery-Cd: Erythrocyte cadmium; Ery-As: Erythrocyte arsenic; Ery-Pb: Erythrocyte lead.
[a] Mann-Whitney *U* test for comparing boys and girls for continuous variables, Pearson's chi-square test for categorical variables.
[b] At 10-year follow-up.
[c] Season of conception categorized as pre-monsoon (March-May), monsoon (June-October), or post-monsoon (November-February).
[d] Adjusted for specific gravity (mean 1.012).

## 3. Results

The general characteristics of the children included in this study, consisting of 52% boys and 48% girls, are summarized in Table 1. At 10 years of age, 42% of the children were underweight (WAZ < -2) and more than a fourth (28%) were stunted (HAZ < -2). Only 11 children (0.72%) were overweight (WAZ > 1 but < 2) and six (0.39%) were obese (WAZ > 2). The girls were slightly lighter than boys from birth until 10 years of age, and shorter at birth up to 5 years but not at 10 years (Supplementary Table S2). Parity was slightly higher in mothers to girls than in mothers to boys when the children were 10 years of age (Table 1), but not at enrollment (p-value = 0.58). No other general characteristics of the mothers or children differed by child gender.

Exposure to As, Cd, and Pb did not differ significantly between boys and girls at any exposure timepoint (Table 1). There were only weak correlations between the studied metals (Supplementary Table S3), with the strongest correlation, although still quite weak, found between maternal concentrations of Ery-Cd and Ery-Pb ($r_S = 0.37$, $p < 0.001$). At 10 years of age, the urinary concentrations of As, Cd and Pb showed very low correlations, if any (Supplementary Table S3). For Cd and Pb, maternal erythrocyte concentrations during early pregnancy and the children's urinary concentrations at 10 years were not correlated, while maternal Ery-As and U-As at 10 years were moderately correlated ($r_S = 0.46$, p-value < 0.001). Spearman's correlations between metal exposure biomarkers, outcome variables at 10 years of age, and covariates are presented in Supplementary Table S3.

Children who lacked gestational exposure data (n = 91) had slightly lower urinary Pb concentrations at 10 years (1.3 μg/L versus 1.6 μg/L; p-value = 0.017) and a disproportionately large portion of them were conceived during the post-monsoon season (75% versus 45%; $p < 0.001$) compared to the ones with available gestational exposure information, while no other differences were observed in other characteristics, and As or Cd exposure at 10 years (Supplementary Table S4). When comparing the mothers of the children included in this study (n = 1530) with the MINIMat mothers whose children were not included [n = 2095 (total number of live births in MINIMat n = 3625)], we found that the mothers of the included children were slightly lighter (mean 45 ± 6.5 kg vs 46 ± 7.0 kg) and shorter (mean 150 ± 5.1 cm vs 150 ± 5.4 cm) and had higher parity (mean 1.5 ± 1.4 vs 1.3 ± 1.3) than the mothers of the children who were not included.

### 3.1. Cross-sectional analyses

We found no significant association between U-As and HAZ at 10 years in the crude or the adjusted models (Table 2). U-Cd was inversely associated with HAZ both in the crude and multivariable-adjusted models, although the estimate decreased by 62% in the adjusted model. A doubling of U-Cd was associated with a decrease in HAZ by −0.046 scores (95% CI: −0.094; 0.0014). The association of U-Cd with HAZ did not vary by gender (Table 2). U-Pb was not associated with HAZ in all children. After stratifying by gender, U-Pb was inversely associated with HAZ in boys, in whom the estimate increased by 34% following adjustment (B: −0.087; 95% CI: −0.15, −0.021), whereas no association was observed in girls (B: 0.036; 95% CI: −0.045, 0.12).

No association was observed between U-As and WAZ at 10 years (Table 2). In the crude linear model (Model 1), U-Cd was inversely associated with WAZ, and this association remained after further adjustment (Model 2), although the estimate decreased by 55% (B: −0.072; 95% CI: −0.12, −0.020). The inverse association was most notable in boys (B: −0.093; 95% CI: −0.17, −0.020), in whom the estimate was twice as high as that observed in girls (B: −0.047; 95% CI: −0.12, 0.029), although both estimates were small. Children's U-Pb was inversely associated with WAZ in the adjusted model (Model 2), although the association was not significant. However, after stratification by gender U-Pb was inversely associated with WAZ in boys (B: −0.084; 95% CI: −0.16, −0.0085), but not in girls (B: 0.051; 95% CI: −0.036, 0.14).

The above associations would imply that the children in the highest tertile of U-Cd were about 0.5 cm shorter and 0.4 kg lighter than the ones in the lowest tertile. After stratification by gender, boys in the highest

**Table 2**
Linear regression models of urinary metal concentrations (arsenic, cadmium, and lead; $log_2$-tranformed) and height-for-age Z-scores (HAZ) and weight-for-age Z-scores (WAZ) at 10 years of age.

| HAZ models[a] | All children | | | Boys | | | Girls | | |
|---|---|---|---|---|---|---|---|---|---|
| | B | 95% CI | p-value | B | 95% CI | p-value | B | 95% CI | p-value |
| **U-As 10y ($log_2$)** | | | | | | | | | |
| Model 1 | −0.0017 | −0.037; 0.034 | 0.93 | −0.0013 | −0.051; 0.048 | 0.96 | −0.0024 | −0.054; 0.049 | 0.93 |
| Model 2 | 0.027 | −0.0056; 0.060 | 0.10 | 0.020 | −0.024; 0.065 | 0.37 | 0.032 | −0.017; 0.080 | 0.20 |
| **U-Cd 10y ($log_2$)** | | | | | | | | | |
| Model 1 | −0.12 | −0.17; −0.065 | <0.001 | −0.14 | −0.21; −0.065 | <0.001 | −0.094 | −0.17; −0.020 | 0.013 |
| Model 2 | **−0.046** | **−0.094; 0.0014** | **0.057** | −0.054 | −0.12; 0.011 | 0.10 | −0.032 | −0.10; 0.038 | 0.37 |
| **U-Pb 10y ($log_2$)** | | | | | | | | | |
| Model 1 | −0.030 | −0.087; 0.027 | 0.30 | −0.065 | −0.14; 0.011 | 0.092 | 0.016 | −0.071; 0.10 | 0.72 |
| Model 2 | −0.032 | −0.084; 0.020 | 0.22 | **−0.087** | **−0.15; −0.021** | **0.010** | 0.036 | −0.045; 0.12 | 0.38 |
| **WAZ models[b]** | | | | | | | | | |
| **U-As 10y ($log_2$)** | | | | | | | | | |
| Model 1 | −0.037 | −0.076; 0.0032 | 0.071 | −0.028 | −0.084; 0.028 | 0.33 | −0.046 | −0.10; 0.010 | 0.11 |
| Model 2 | 0.013 | −0.023; 0.049 | 0.49 | 0.014 | −0.036; 0.064 | 0.59 | 0.0094 | −0.043; 0.062 | 0.72 |
| **U-Cd 10y ($log_2$)** | | | | | | | | | |
| Model 1 | −0.16 | −0.22; −0.10 | <0.001 | −0.19 | −0.27; −0.11 | <0.001 | −0.13 | −0.21; −0.050 | 0.002 |
| Model 2 | **−0.072** | **−0.12; −0.020** | **0.007** | **−0.093** | **−0.17; −0.020** | **0.013** | −0.047 | −0.12; 0.029 | 0.22 |
| **U-Pb 10y ($log_2$)** | | | | | | | | | |
| Model 1 | −0.0035 | −0.067; 0.060 | 0.92 | −0.056 | −0.14; 0.029 | 0.20 | 0.066 | −0.029; 0.16 | 0.17 |
| Model 2 | −0.025 | −0.082; 0.032 | 0.39 | **−0.084** | **−0.16; −0.0085** | **0.029** | 0.051 | −0.036; 0.14 | 0.25 |

Abbreviations: U-As: total urinary arsenic; U-Cd: urinary cadmium; U-Pb: urinary lead; CI: confidence interval.
Model 1: crude model.
Model 2: adjusted for child gender, age at 10y (years), maternal parity (number of children), maternal education (years) and the family's socioeconomic status (quintiles) at the 10-year follow-up, and maternal height (cm) in HAZ models and maternal weight (kg) at gestational week 8 in WAZ models.
[a] Total number of children 1523; 800 boys and 723 girls.
[b] Total number of children 1520; 798 boys and 722 girls.

tertile of U-Cd were 0.6 kg lighter than the ones in the lowest. The boys in the highest tertile of U-Pb were about 0.7 cm shorter and 0.4 kg lighter than the boys in the lowest tertile of exposure.

In sensitivity analysis, including all urinary metal concentrations in the same model, we found no noteworthy changes in the associations between any of the metals and HAZ (Supplementary Table S5, Model 3). Neither was there any change in the associations with WAZ, with the exception of the association between U-Pb and WAZ in boys, which was slightly weakened, although still close to statistical significance (Supplementary Table S6, Model 3). Adjustment for categories of supplementation during pregnancy did not affect any of the associations between exposure biomarkers and HAZ or WAZ (Supplementary Tables S5 and S6, Model 4).

### 3.2. Maternal metal exposure during early pregnancy and anthropometry at 10 years

In the crude linear regression model (Table 3; Model 1), maternal Ery-As in early pregnancy was significantly inversely associated with HAZ at 10 years of age, but further adjustment decreased the estimate by 62% and it was no longer significant. Maternal Ery-Cd was inversely associated with HAZ in the crude model (Model 1), but this association was attenuated after further adjustment. We found no association between maternal Ery-Pb and HAZ at 10 years of age.

As with HAZ, maternal Ery-As was inversely associated with WAZ at 10 years of age in the crude linear model (Table 3; Model 1), but again the association was attenuated after further adjustment. Neither maternal Ery-Cd nor Ery-Pb was associated with child WAZ at 10 years in the adjusted models (Table 3). None of the associations with either HAZ or WAZ differed by child gender. Further adjustment for the other metals included in this study, or for the supplementation provided to the mother during pregnancy, did not affect any of the associations (Supplementary Tables S7 and S8, Models 3 and 4).

### 3.3. Longitudinal analyses

In the longitudinal regression analyses based on maternal exposure in early pregnancy and growth data from birth to 10 years of age, both maternal Ery-As and Ery-Cd concentrations were inversely associated with childhood HAZ in the crude models (Table 4, Model 1). However, following adjustments (Model 2), the estimates decreased markedly, and none of the associations were found to be statistically significant. None of the metal-related associations with HAZ during childhood differed by child gender.

Maternal Ery-As concentrations in early pregnancy were inversely associated with WAZ during childhood in the crude model (Table 7, Model 1), but the estimate was attenuated after adjustment (Model 2). Maternal Ery-Cd was inversely associated with WAZ during childhood in the crude model, although the estimate decreased by 56% following adjustment (Model 2) and it was no longer significant. Following stratification by gender (Table 4), maternal Ery-Cd was significantly inversely associated with WAZ during childhood in boys (B: −0.071; 95% CI: −0.14, −0.0047), whereas no association was observed in girls (B: 0.0094; 95% CI: −0.060, 0.079). Maternal Ery-Pb was not found to be associated with WAZ during childhood either in all children or after stratifying for gender. Repeating the models above with Ery-Cd categorized into tertiles, boys of mothers in the highest tertile of Ery-Cd were on average 0.1 kg lighter during their first 10 years in life than the boys of mothers in the lowest tertile of exposure.

When all metals were included in the same model, we found no changes in the associations between the metals and HAZ during childhood (Supplementary Table S9, Model 3). However, the association between Ery-Cd and WAZ in boys became weaker and was no longer statistically significant (Supplementary Table S10, Model 3). Further adjustment for the supplementation provided during pregnancy did not affect any of the associations (Supplementary Tables S9 and S10, Model 4).

**Table 3**
Linear regression models of the mothers' erythrocyte metal concentrations in early pregnancy (arsenic, cadmium, and lead; $log_2$-transformed) and height-for-age Z-scores (HAZ) and weight-for-age Z-scores (WAZ) at 10 years of age.

| HAZ models[a] | All children | | | Boys | | | Girls | | |
|---|---|---|---|---|---|---|---|---|---|
| | B | 95% CI | p-value | B | 95% CI | p-value | B | 95% CI | p-value |
| **Ery-As GW14 ($log_2$)** | | | | | | | | | |
| Model 1 | −0.039 | −0.074; −0.0040 | 0.029 | −0.027 | −0.075; 0.020 | 0.26 | −0.053 | −0.10; −0.00039 | 0.048 |
| Model 2 | −0.015 | −0.047; 0.018 | 0.37 | −0.012 | −0.054; 0.030 | 0.58 | −0.022 | −0.073; 0.028 | 0.38 |
| **Ery-Cd GW14 ($log_2$)** | | | | | | | | | |
| Model 1 | −0.075 | −0.13; −0.024 | 0.004 | −0.075 | −0.15; −0.0016 | 0.045 | −0.079 | −0.15; −0.0059 | 0.034 |
| Model 2 | −0.011 | −0.061; 0.039 | 0.66 | 0.00051 | −0.067; 0.068 | 0.99 | −0.016 | −0.089; 0.057 | 0.67 |
| **Ery-Pb GW14 ($log_2$)** | | | | | | | | | |
| Model 1 | −0.030 | −0.086; 0.027 | 0.30 | −0.0033 | −0.080; 0.073 | 0.93 | −0.062 | −0.15; 0.021 | 0.14 |
| Model 2 | −0.017 | −0.071; 0.037 | 0.54 | 0.0083 | −0.062; 0.079 | 0.82 | −0.046 | −0.13; 0.036 | 0.27 |
| **WAZ models**[b] | | | | | | | | | |
| **Ery-As GW14 ($log_2$)** | | | | | | | | | |
| Model 1 | −0.047 | −0.086; −0.0077 | 0.019 | −0.017 | −0.070; 0.037 | 0.54 | −0.081 | −0.14; −0.024 | 0.005 |
| Model 2 | 0.0026 | −0.033; 0.038 | 0.89 | 0.020 | −0.027; 0.067 | 0.40 | −0.018 | −0.072; 0.037 | 0.53 |
| **Ery-Cd GW14 ($log_2$)** | | | | | | | | | |
| Model 1 | −0.053 | −0.11; 0.0051 | 0.074 | −0.088 | −0.17; −0.0062 | 0.035 | −0.022 | −0.10; 0.059 | 0.60 |
| Model 2 | 0.030 | −0.024; 0.085 | 0.27 | 0.0046 | −0.071; 0.081 | 0.91 | 0.062 | −0.016; 0.14 | 0.12 |
| **Ery-Pb GW14 ($log_2$)** | | | | | | | | | |
| Model 1 | 0.029 | −0.034; 0.092 | 0.37 | 0.043 | −0.043; 0.13 | 0.32 | 0.010 | −0.082; 0.10 | 0.81 |
| Model 2 | 0.024 | −0.034; 0.083 | 0.42 | 0.020 | −0.058; 0.098 | 0.61 | 0.026 | −0.062; 0.11 | 0.56 |

Abbreviations: Ery-As: erythrocyte arsenic; GW: gestational week; Ery-Cd: erythrocyte cadmium; Ery-Pb: erythrocyte lead; CI: confidence interval.
Model 1: crude model.
Model 2: adjusted for child gender, age at 10y (years), season of conception (pre-monsoon, monsoon, or post-monsoon), and the family's socioeconomic status (quintiles), maternal parity (number of children) and maternal education (years) at enrollment, and maternal height (cm) in HAZ models and maternal weight (kg) at gestational week 8 in WAZ models.
[a] Total number of children 1438; 755 boys and 683 girls.
[b] Total number of children 1435; 753 boys and 682 girls.

**Table 4**
Multivariate linear regression models of the mothers' erythrocyte metal concentrations during early pregnancy (arsenic, cadmium, and lead; $log_2$-transformed) and height-for-age Z-scores (HAZ) and weight-for-age Z-scores (WAZ) from birth to 10 years of age (19 measurements).

| HAZ models[a] | All children | | | Boys | | | Girls | | |
|---|---|---|---|---|---|---|---|---|---|
| | B | 95% CI | p-value | B | 95% CI | p-value | B | 95% CI | p-value |
| **Ery-As GW14 ($log_2$)** | | | | | | | | | |
| Model 1 | −0.033 | −0.067; 0.00095 | 0.057 | −0.027 | −0.076; 0.021 | 0.27 | −0.040 | −0.087; 0.0080 | 0.10 |
| Model 2 | −0.012 | −0.042; 0.017 | 0.41 | −0.016 | −0.058; 0.025 | 0.44 | −0.0076 | −0.049; 0.034 | 0.72 |
| **Ery-Cd GW14 ($log_2$)** | | | | | | | | | |
| Model 1 | −0.060 | −0.11; −0.0095 | 0.020 | −0.081 | −0.15; −0.010 | 0.025 | −0.036 | −0.11; 0.035 | 0.32 |
| Model 2 | −0.0087 | −0.057; 0.039 | 0.72 | −0.026 | −0.096; 0.044 | 0.47 | 0.017 | −0.050; 0.083 | 0.63 |
| **Ery-Pb GW14 ($log_2$)** | | | | | | | | | |
| Model 1 | 0.017 | −0.038; 0.072 | 0.55 | 0.012 | −0.062; 0.087 | 0.74 | 0.025 | −0.057; 0.11 | 0.55 |
| Model 2 | 0.024 | −0.029; 0.077 | 0.37 | 0.024 | −0.051; 0.099 | 0.53 | 0.033 | −0.043; 0.11 | 0.39 |
| **WAZ models[b]** | | | | | | | | | |
| **Ery-As GW14 ($log_2$)** | | | | | | | | | |
| Model 1 | −0.036 | −0.068; −0.0030 | 0.032 | −0.015 | −0.060; 0.030 | 0.51 | −0.059 | −0.11; −0.011 | 0.016 |
| Model 2 | 0.0017 | −0.027; 0.031 | 0.91 | 0.014 | −0.024; 0.052 | 0.47 | −0.012 | −0.055; 0.032 | 0.60 |
| **Ery-Cd GW14 ($log_2$)** | | | | | | | | | |
| Model 1 | −0.078 | −0.13; −0.027 | 0.003 | −0.12 | −0.19; −0.055 | <0.001 | −0.035 | −0.11; 0.039 | 0.35 |
| Model 2 | −0.034 | −0.082; 0.015 | 0.18 | **−0.071** | **−0.14; −0.0047** | **0.036** | 0.0094 | −0.060; 0.079 | 0.79 |
| **Ery-Pb GW14 ($log_2$)** | | | | | | | | | |
| Model 1 | 0.013 | −0.042; 0.068 | 0.65 | −0.0080 | −0.079; 0.063 | 0.82 | 0.037 | −0.049; 0.12 | 0.40 |
| Model 2 | −0.016 | −0.067; 0.035 | 0.53 | −0.046 | −0.11; 0.019 | 0.16 | 0.022 | −0.057; 0.10 | 0.58 |

Abbreviations: Ery-As: erythrocyte arsenic; GW: gestational week; Ery-Cd: erythrocyte cadmium; Ery-Pb: erythrocyte lead; CI: confidence interval.
Model 1: crude model.
Model 2: adjusted for child gender, age of the child in months (5 splines), season of conception (pre-monsoon, monsoon, or post-monsoon), and the family's socio-economic status (quintiles), maternal parity (number of children) and maternal education (years) at enrollment, and maternal height (cm) in HAZ models and maternal weight (kg) at gestational week 8 in WAZ models.
[a] Total number of children 1438; 755 boys and 683 girls.
[b] Total number of children 1436; 754 boys and 682 girls.

## 4. Discussion

We present herein a large longitudinal study with a remarkably long follow-up time elucidating the relationship between gestational and childhood metal exposure and anthropometry at 10 years of age, including growth from birth up to 10 years. To our knowledge, there are no other studies on the relationship between exposure to As or Cd and anthropometry or growth past preschool age. The boys' life-long Cd exposure, measured by U-Cd, was inversely associated with their WAZ, and possibly also HAZ, at 10 years of age, whereas no associations were observed in girls. Likewise, the boys', but not the girls', concurrent Pb exposure was inversely associated with their WAZ and HAZ, although when controlling for Cd exposure the association with WAZ was less certain. The mothers' Cd exposure in early pregnancy was inversely associated with the boys' WAZ during early childhood. Concerning As exposure, we found no significant associations with child anthropometry measures, despite the high exposure in many of the children, both during gestation and in childhood.

Following our initial findings concerning Cd-exposed children in the MINIMat cohort (Kippler et al. 2012a; Kippler et al. 2012c), several other studies have also reported maternal Cd exposure in pregnancy to be inversely associated with birth size, especially in girls (Cheng et al. 2017; Rollin et al. 2015; Romano et al. 2016; Taylor et al. 2016; Zhang et al. 2018). In the 5-year follow-up of these MINIMat children, their U-Cd was inversely associated with WAZ and HAZ, and as previously observed at birth, the associations were more apparent in girls than boys (Gardner et al. 2013). However, gestational exposure was not associated with WAZ or HAZ at 5 years, possibly because it was based on maternal U-Cd, while the specific ongoing exposure during pregnancy (e.g., blood Cd) was not assessed. Still, in a longitudinal study of 515 Greek mother–child pairs, elevated maternal U-Cd [comparing the third tertile (0.57–2.7 μg/L) to the two lower tertiles (<0.57 μg/L)] in early pregnancy was associated with slower weight trajectories up to 4 years in all children, and slower height trajectories in girls (Chatzi et al. 2018). However, 16% of the women in that cohort were smoking during early pregnancy. In the longitudinal analysis in the present study, the mothers' (all non-smokers) Ery-Cd in early pregnancy, reflecting ongoing exposure, was inversely associated with the boys' WAZ during childhood. The impact of gestational exposure on child growth appeared to decline with time as the mother's Ery-Cd during early pregnancy was not associated with either WAZ or HAZ at 10 years. Instead, the childhood exposure (median U-Cd 0.24 μg/L, 5-95th percentile 0.083–0.64 μg/L) was associated with a modest decrease in the anthropometric measures in all children at 10 years which was evident particularly in boys, corresponding to an approximate difference of 0.6 kg in weight between the boys in the highest and lowest tertile of Cd exposure. The indicated shift in gender-susceptibility towards Cd from early childhood to pre-pubertal age is notable, and it requires confirmation in other observational studies. Indeed, studies on neurological endpoints in relation to Cd exposure seem to indicate that boys are somewhat more susceptible than girls at school-age (Ciesielski et al. 2012; Gustin et al. 2018).

We observed that the boys' ongoing Pb exposure (median U-Pb 1.5 μg/L, 5-95th percentile 0.62–4.1 μg/L) at 10 years was inversely associated with their HAZ and WAZ, with a doubling of U-Pb, for example from the mean concentration of 1.9 μg/L to 3.8 μ/L, corresponding to a decrease of about 0.085 scores of both HAZ and WAZ, and a difference of about 0.7 cm and 0.4 kg between boys in the highest and lowest tertile of Pb exposure. Similar findings have been reported in a cross-sectional Chinese study including 1678 children below 6 years of age, in which blood Pb concentrations (mean blood Pb 4.6 μg/dL) were inversely associated with HAZ and WAZ in boys, but not in girls (Zhou et al. 2020). We have not come across any other studies which have reported gender differences, except for a small (n = 259) cross-sectional study of 7-year-old Uruguayan children, which found a suggested inverse association between blood Pb concentrations (mean 4.2 μg/dL, range 0.8–7.8 μg/dL) and Body Mass Index-for-age Z-scores in girls, but not in boys (Donangelo et al. 2021). However, in a longitudinal study of 481

Russian boys with yearly anthropometric measurements from 8 to18 years of age, boys with blood Pb concentrations ≥ 5 μg/dL were shorter during the whole study period than children with blood Pb < 5 μg/dL at baseline (overall median 3.0 μg/dL, range 0.5–31 μg/dL) (Burns et al. 2017). The largest difference was observed between 12 and 15 years of age, which amounted to a decrease of 0.52 scores in HAZ, and a final difference of 0.34 scores at 18 years corresponding to 2.6 cm lower height. In a cross-sectional Polish study of 7–15-year-olds in a contaminated area (n = 899), blood Pb (mean blood Pb 7.7 μg/dL) was inversely associated with weight and height (Ignasiak et al. 2006). Unfortunately, blood Pb concentrations of the children in the present study, which would have enabled a direct dose–response comparison with other studies, were not available at 10 years of age. However, in a sub-sample (n = 215) of these children at 9 years of age, their median blood Pb concentration was 4.4 μg/dL [(estimated from their median erythrocyte concentration according to (Gustin et al. 2020)], and 7.2 μg/dL at 4.5 years of age (unpublished data), which is comparable to the aforementioned studies.

As mentioned in a recent review (Rahman et al. 2017), most of the literature about As exposure and children's size and/or growth originates from Bangladesh, and from the MINIMat cohort which is also investigated herein. In this cohort, maternal U-As was inversely associated with birth weight and head- and chest circumference, but not birth length (Rahman et al. 2009). In the follow-ups at 1.5–2 years (Saha et al. 2012) and 5 years of age (Gardner et al. 2013), the children's U-As was inversely associated with their weight and height, and the associations were more pronounced in girls than in boys, while no associations were observed with the mother's U-As concentrations in early pregnancy. Also, the effect size was smaller at 5 years than at 2 years. In this follow-up at 10 years of age, we did not find any association between the concurrent or gestational As exposure and anthropometry up to 10 years of age, indicating that child growth becomes less susceptible to As with increasing age. This is surprising, considering the elevated continuous As exposure through drinking water (range < 0.01–672 μg/L, with 40% over the WHO guideline value of 10 μg/L) and food in many of the families (Kippler et al. 2016b), and the fact that many of the children were malnourished, which is likely to render them more susceptible to toxic insult. Still, the As may cause other adverse health effects, which is why mitigation efforts are highly desirable.

Pb and, to a lesser extent, Cd have been found to accumulate in bone (EFSA 2009; 2013) and both metals seem to interfere with calcium homeostasis (Goyer 1996) and bone remodeling and elongation (Brzoska et al. 2005; Pounds et al. 1991), which in turn may lead to impaired growth. In a cross-sectional Chinese study (Yang et al. 2013), including 246 children aged 3–8 years in an e-waste recycling area, blood Pb concentrations (mean blood Pb 7.3 μg/dL) were inversely associated with weight and height. Simultaneously, blood Pb was positively associated with urinary deoxypyridinoline (DPD), a biomarker of bone resorption, suggesting that the Pb exposure reduced bone mineral density. In experimental studies, Pb exposure has been shown to alter growth plate chondrogenesis and longitudinal growth (Beier et al. 2015; Hamilton and O'Flaherty 1994; Hicks et al. 1996; Tomaszewska et al. 2016; Zuscik et al. 2007). As for Cd, Yang and coworkers (2013) found no association of ongoing Cd exposure (blood Cd) with either anthropometry or bone biomarkers. However, in a study of Pakistani children aged 8–12 years, their long-term Cd exposure (U-Cd) was associated with increased urinary DPD levels (Sughis et al. 2011). In 504 9-year-old children in another branch of the MINIMat cohort, U-Cd was positively associated with urinary DPD in all children, whereas U-Cd and serum osteocalcin (a biomarker of bone formation) were positively associated in girls and inversely associated in boys, suggesting an increased disruption of the feedback loop between bone resorption and formation in boys (Malin Igra et al. 2019). The latter gender-specific association with osteocalcin may potentially be a part in explaining why the present findings are restricted to boys' anthropometry measures at 10 years of age (Malin Igra et al. 2019). Another potential mode of action for Cd and Pb may be through endocrine disruption of growth-related hormones such as thyroid hormones and sex hormones (Choe et al. 2003; Darbre 2006; Johnson et al. 2003), which may impair child growth in a gender-specific manner.

The main strengths of this study include the large number of participating children and their mothers, all non-smokers, and that anthropometric measurements were available at as many as 19 time points during a remarkable follow-up time of 10 years. Also, we have individual metal exposure assessment both for the mothers during pregnancy and for the children. On the other hand, it should be noted as a limitation that U-As and U-Pb are short-term markers of exposure which may be prone to day-to-day variation (Sommar et al. 2014; Vahter 2002), although the actual exposure through food and drinking water remained rather stable (Bergkvist et al. 2010; Kippler et al. 2016b). Furthermore, we have previously shown that the concentrations of As and Pb in urine and blood, the latter having a half-life of months, are well correlated (Bergkvist et al. 2010; Gardner et al. 2011). It would also have been beneficial to have erythrocyte or blood concentrations of all the three studied metals at 10 years in order to assess time-varying exposure. A further limitation is that data concerning environmental tobacco smoke, which can be an additional source of metal exposure (Vardavas et al. 2011), was not available at this 10-year follow-up. Although all mothers were non-smokers, other family members might have smoked indoors. Another factor which may have complicated discerning the true associations between metal exposures and growth at 10 years is that the children are on the verge of entering puberty, and therefore close to starting the growth spurt associated with it. Indeed, in another branch of the MINIMat cohort 11% of the girls had reached puberty at 10 years of age (Svefors et al. 2016). Finally, we cannot exclude that our findings are influenced by residual or unmeasured confounding. SES has for example changed for some families from enrollment to 10 years later. SES is an important predictor of growth, because of food security, and also exposure, especially to As, due to the economic possibility of affording new deep wells with lower As concentrations (Kippler et al. 2016b). Also, SES is linked to Cd exposure, as affording a more varied diet less reliant on rice would limit the exposure (Kippler et al. 2010).

## 5. Conclusions

We found that children's long-term Cd exposure was linked to lower WAZ, and possibly HAZ, at 10 years of age, and that early gestational Cd exposure was linked to decreased WAZ during childhood. Associations were stronger in boys than in girls, contrary to findings at earlier ages (Gardner et al. 2013; Kippler et al. 2012a). Concurrent Pb exposure was linked to lower WAZ and HAZ at 10 years in boys, but not in girls. Despite the high environmental exposure to arsenic in this cohort, both during gestation and childhood, no associations were found with either child anthropometry or growth up to 10 years of age. None of the findings are likely of concern at an individual level, as the effect estimates were small, but unfavorable in a population already suffering from other important determinants of child growth, such as maternal and child malnutrition, and low SES and maternal education. To note, the inverse association between early-life Pb exposure and growth does not appear to be as critical as its association with neurotoxicity (EFSA 2013). The results concerning Cd add to the growing evidence that Cd exposure in early life does have an influence on health and development. This should be considered during future health risk assessment, as many millions of people around the world are reliant on a diet primarily based on rice and therefore exposed to comparable Cd levels.

## CRediT authorship contribution statement

**Annachiara Malin Igra:** Data curation, Formal analysis, Methodology, Visualization, Writing - original draft, Writing - review & editing. **Anna Warnqvist:** Formal analysis, Methodology, Writing - original

draft, Writing - review & editing. **Syed Moshfiqur Rahman:** Data curation, Project administration, Writing - review & editing. **Eva-Charlotte Ekström:** Project administration, Funding acquisition, Methodology, Writing - review & editing. **Anisur Rahman:** Resources, Data curation, Writing - review & editing. **Marie Vahter:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing - review & editing. **Maria Kippler:** Conceptualization, Funding acquisition, Data curation, Project administration, Methodology, Supervision, Writing - review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106738.

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