Environment International 139 (2020) 105723

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Prenatal and childhood arsenic exposure through drinking water and food and cognitive abilities at 10 years of age: A prospective cohort study

Marie Vahter[a], Helena Skröder[a], Syed Moshfiqur Rahman[b,c], Michael Levi[a], Jena Derakhshani Hamadani[c], Maria Kippler[a,*]

[a] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[b] International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh
[c] International Maternal and Child Health, Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

ARTICLE INFO

Handling Editor: Olga-Ioanna Kalantzi

Keywords:
Arsenic exposure
Neurotoxicity
Child development
Cognition
School-age
Gender differences

ABSTRACT

Background: Our studies of children in a rural Bangladeshi area, with varying concentrations of arsenic in well-water, indicated modest impact on child verbal cognitive function at 5 years of age.
Objectives: Follow-up of arsenic exposure and children's cognitive abilities at school-age.
Methods: In a nested sub-cohort of the MINIMat supplementation trial, we assessed cognitive abilities at 10 years of age (n = 1523), using Wechsler Intelligence Scale for Children (WISC-IV). Arsenic in maternal urine and erythrocytes in early pregnancy, in child urine at 5 and 10 years, and in hair at 10 years, was measured using Inductively Coupled Plasma Mass Spectrometry.
Results: Median urinary arsenic at 10 years was 58 μg/L (range 7.3–940 μg/L). Multivariable-adjusted regression analysis showed that, compared to the first urinary arsenic quintile at 10 years (< 30 μg/L), the third and fourth quintiles (30–45 and 46–73 μg/L, respectively) had 6–7 points lower Full developmental raw scores (B: −7.23, 95% CI −11.3; −3.18, and B: −6.37, 95% CI −10.5; −2.22, respectively), corresponding to ~0.2 SD. Verbal comprehension and Perceptual reasoning seemed to be affected. Models with children's hair arsenic concentrations showed similar results. Maternal urinary arsenic in early pregnancy, but not late pregnancy, showed inverse associations with Full developmental scores (quintiles 2–4: B: −4.52, 95% CI −8.61; −0.43, B: −5.91, 95% CI −10.0; −1.77, and B: −5.98, 95%CI −10.2; −1.77, respectively, compared to first quintile), as well as with Verbal comprehension, Perceptual reasoning, and Processing speed, especially in girls ($p < 0.05$ for interaction of sex with Full developmental scores and Perceptual reasoning). In models with all exposure time points included, both concurrent exposure at 10 years and early prenatal exposure remained associated with cognitive abilities.
Conclusions: Both early prenatal and childhood arsenic exposure, even at low levels (about 50 μg/L in urine), was inversely associated with cognitive abilities at school-age, although the estimates were modest.

1. Introduction

Exposure to inorganic arsenic, a known carcinogenic toxicant, through drinking water and certain food is common world-wide (EFSA, 2014; IARC, 2012). Most of our knowledge regarding the toxic effects of arsenic is based on studies in exposed adults, but there is increasing evidence that early-life exposure may be especially perilous. In particular, arsenic exposure prenatally and/or in early childhood seems to affect the developing immune system (Ahmed et al., 2014; Attreed et al., 2017; Farzan et al., 2016; Raqib et al., 2017), impair fetal and childhood growth (Gardner et al., 2013; Rahman et al., 2017a), and increase the risk of later life cancer (Roh et al., 2018; Steinmaus et al., 2014). Several, mainly cross-sectional studies, have reported inverse associations between arsenic exposure and cognitive abilities in children (Rocha-Amador et al., 2007; Rodrigues et al., 2016; Rosado et al., 2007; Wang et al., 2007; Wasserman et al., 2007; Wasserman et al., 2011; von Ehrenstein et al., 2007), even at low-to-moderate exposure (Signes-Pastor et al., 2019; Wasserman et al., 2014), although not consistently (Desai et al., 2018; Khan et al., 2012; Kordas et al., 2015).

Our large prospective studies in a rural area in Bangladesh, where

Abbreviations: BMI, body mass index; BAZ, body mass index z-score; GW, gestational week; HG, hydride generation; ICP-MS, Inductively Coupled Plasma Mass Spectrometry; Q, quintile

* Corresponding author at: Institute of Environmental Medicine, Karolinska Institutet, Box 210, SE-171 77 Stockholm, Sweden.
E-mail address: maria.kippler@ki.se (M. Kippler).

https://doi.org/10.1016/j.envint.2020.105723
Received 16 December 2019; Received in revised form 3 April 2020; Accepted 3 April 2020
Available online 13 April 2020

elevated arsenic concentrations in drinking water are frequent, showed no significant association between pre- or postnatal arsenic exposure (based on maternal and child urinary arsenic) and child development at 7 or 18 months of age (Hamadani et al., 2010; Tofail et al., 2009). At 5 years of age, however, we found a modest inverse association between particularly the children's concurrent urinary arsenic and their cognitive abilities (Hamadani et al., 2011). Because there has been a continued arsenic exposure through drinking water and also through food in many families, despite major mitigation efforts over the last 15–20 years (Kippler et al., 2016), we hypothesized that this continued exposure had affected the children's cognitive abilities further. The aim of this study was therefore to assess cognitive abilities at 10 years of age in relation to arsenic exposure, both prenatally and at 5 and 10 years. Based on the knowledge about arsenic susceptibility factors and our findings of gender-differences in early life arsenic toxicity (Broberg et al., 2014; Gardner et al., 2013; Hamadani et al., 2011), we also evaluated whether arsenic would affect the development differently in boys and girls.

2. Methods

2.1. Study area and population

Details concerning the study area and population are given in our previous publications (Gustin et al., 2018; Rahman et al., 2017b; Skroder et al., 2017a). In short, the study was conducted in Matlab, a rural area 53 km southeast of the capital Dhaka. Since more than 50 years, the International Center for Diarrhoeal Disease Research, Bangladesh (icddr,b) continuously collects vital health and demographic information in the area. In 2002–2003, a parallel water-screening project found that 70% of all the functioning tube wells, used by more than 95% of the population, had arsenic concentrations exceeding 10 μg/L (Rahman et al., 2006). At the initiation of the cohort, pumps were painted red if the arsenic concentration in the well water exceeded the national drinking water standard of 50 μg/L. Pregnant women and people showing symptoms of arsenic intoxication were given priority for mitigation efforts, performed in collaboration with NGOs (Rahman et al., 2006).

Our studies concerning child health and development in relation to early-life exposure to various toxicants were nested in a population-based randomized trial [Maternal and Infant Nutrition Intervention in Matlab (MINIMat)], evaluating the effects of food and micronutrient supplementation in pregnancy (Persson et al., 2012). In total 4436 women were recruited in early pregnancy and randomly assigned to two food supplementations and three micronutrient supplementations (Persson et al., 2012). The food supplementation (608 kcal of energy, vegetable-based, provided six days a week) was initiated either directly after recruitment or according to common practice around gestational week (GW) 20. The randomized micronutrient supplementation was initiated at GW 14 and consisted of either: (i) 30 mg iron and 400 μg folic acid, (ii) 60 mg iron and 400 μg folic acid (WHO's standard supplementation for pregnant women), or (iii) a multiple micronutrient capsule containing 30 mg iron and 400 μg folic acid, as well as 13 other micronutrients.

Infants born in the MINIMat cohort between May 2002 and December 2003 (n = 2853) were included in the child development project. More than 2000 children were tested at 7 months and 1.5 and 5 years of age (Hamadani et al., 2010; Hamadani et al., 2011; Tofail et al., 2009). For the follow-up at 10 years of age, we invited children who *i*) were born within MINIMat cohort between October 2002 and December 2003, *ii*) had participated in the developmental testing at both 1.5 and 5 years of age, and *iii*) were alive and registered as residents in the study area at 10 years of age (n = 1607). Out of those, 1530 (95%) agreed to participate in the follow-up of developmental testing. The main reasons for loss to follow-up were out-migration and parents' refusal. Spot urine samples for assessment of arsenic exposure were obtained from 1523 of the tested children and hair samples from 1452 children. We had urinary arsenic data for 1477 children at 5 years and for 1467 mothers in GW 8 and for 1389 mother in GW 30. For 1439 mothers we also had blood arsenic (erythrocyte fraction) in GW14.

Written consent was obtained from mothers at enrollment and again before the testing of the 10-year-olds. The project was approved by the research and ethical review committees at icddr,b, Dhaka, Bangladesh, and the Regional Ethical Review Board in Stockholm, Sweden.

2.2. Exposure assessment

We have previously reported that also food, mainly rice, contributes to inorganic arsenic exposure in the present cohort (Gardner et al., 2011a, Kippler et al., 2016), and therefore we used biomarkers of exposure that reflect the total ingestion of arsenic from all sources. Inorganic arsenic is metabolized in the body by methylation (through the one carbon metabolism cycle) producing methylarsonic acid (MMA) and dimethylarsinic acid (DMA), which are excreted in urine together with a certain amount of inorganic arsenic. The sum of the metabolites in urine is a useful measure of the ongoing individual exposure to inorganic arsenic from all sources (Vahter 2002). Total arsenic in urine and blood may overestimate the exposure to inorganic arsenic, as particularly seafood often contains much less toxic organic arsenic compounds, such as arsenobetaine, the arsenic analogue of the osmolyte glycine betaine (EFSA, 2014). However, in the present population the consumption of seafood is very low, and the limited amount of fish consumed generally comes from the rivers, ponds and paddy fields (Hossain et al., 2018), and therefore contain much less arsenic than marine fish. Consequently, the sum concentrations of metabolites of inorganic arsenic in maternal urine were found to correlate strongly with the concentrations of total arsenic in urine (R^2 = 0.96, $p < 0.001$, n = 290) and blood (R^2 = 0.83, $p < 0.001$, n = 265) (Gardner et al., 2011b). We later measured both arsenic metabolites and total arsenic in urine of more mothers and children, with excellent agreement (R^2 = 0.90, $p < 0.0001$, n = 1120, and R^2 = 0.87$p < 0.0001$, n = 1477, respectively). In summary, total urinary and blood arsenic concentrations reflect the exposure to inorganic arsenic very well in the present population.

In the present study, assessment of prenatal exposure was based on the sum of arsenic metabolites (as we had those measures for more mothers) in spot urine samples at GW 8 and 30 (to evaluate potential critical prenatal exposure periods), as well as total arsenic in blood (erythrocyte fraction) at GW 14 (Gardner et al., 2011b). While the half-life of arsenic in the whole body is very short (few days for excretion in urine), arsenic in erythrocytes reflects arsenic during the lifetime of the erythrocytes, i.e. the previous 3–4 months. Assessment of the children's arsenic exposure was based on measures of total arsenic in spot urine samples at 5 and 10 years of age (Gustin et al., 2018), as well as arsenic in children's hair (2 cm closest to the scalp) at 10 years of age, reflecting exposure to arsenic during previous 2–3 months (Skroder et al., 2017b).

Urine samples from the mothers were analyzed for the sum of metabolites of inorganic arsenic (inorganic arsenic, MMA and DMA) using hydride-generation atomic-absorption spectroscopy (HG-AAS), as described in detail elsewhere (Vahter et al., 2006a). No sample had a concentration below the limit of detection (LOD, mean 1.3 ± 0.27 μg/L across the analytical runs). The children's urine samples were analyzed for total arsenic using inductively coupled plasma mass spectrometry (ICP-MS, Agilent 7500ce and 7700x, Agilent Technologies, Tokyo, Japan) (Gardner et al., 2011a; Kippler et al., 2016). The LOD (three times the standard deviation of the reagent blanks) was < 0.05 and < 0.02 μg/L for the analyses including the urine samples at 5 and 10 years, respectively, and no sample was below these limits. As quality control, two commercial reference materials were included together with the urine samples at 5 years (Seronorm™ Trace Elements Urine Blank, LOT OK4636 and Seronorm™ Trace Elements Urine, LOT NO2525) and at 10 years of age (Seronorm™ Trace Elements Urine, LOT

1011644 and Seronorm™ Trace Elements Urine, LOT 1011645). The obtained concentrations of arsenic were in general in good agreement with the reference values, both in the analytical runs with the urine samples of the 5-year-olds [95 ± 5 μg/L (reference value 85 ± 5 μg/L) and 178 ± 7 μg/L (reference value 184 ± 17 μg/L)] and those of the 10-year-olds [77 ± 4 μg/L (reference value 79 ± 16 μg/L) and 175 ± 9 μg/L (reference value 184 ± 37 μg/L)]. To compensate for the variation in dilution of the urine samples, we adjusted for the specific gravity (SG) of the urine, measured by a digital refractometer (EUROMEX RD712 Clinical Refractometer, Holland), according to urinary arsenic × (mean SG-1)/(individual SG-1), as described previously (Nermell et al., 2008). This is a more suitable adjustment method than creatinine adjustment, as the creatinine excretion is influenced by age, pregnancy, and nutrition (Nermell et al., 2008).

Arsenic in erythrocyte samples was measured using ICP-MS (Agilent 7700x, Agilent Technologies) after alkali dilution, as previously reported (Lu et al., 2015). The LOD was < 0.01 μg/L, and no sample was below LOD. Quality control was performed by including two commercial reference materials for blood (Seronorm™ Trace Elements Whole Blood L-1, LOT 1103128, and L-2, LOT 1103129), and the obtained values (2.3 ± 0.2 μg/L and 13.5 ± 0.5 μg/L) were in good agreement with the reference values (2.4 ± 0.5 μg/L and 14.3 ± 2.9 μg /L). Some of the blood samples included in the present study had previously been analyzed with ICP-MS following acid digestion (Gardner et al., 2011b), and the results from the two analytical methods were highly correlated. However, the arsenic concentrations from the alkali method were consistently 5% lower than those from the acidic method (Lu et al., 2015), and therefore, arsenic concentrations derived using the acidic method were multiplied by 0.95. As described in detail elsewhere, arsenic in hair was measured by ICP-MS (Agilent 7700x, Agilent Technologies) after acid digestion (Skroder et al., 2017b).

2.3. Measurement of cognitive abilities

As previously described (Gustin et al., 2018; Rahman et al., 2017b; Skroder et al., 2017a), children were tested using the Wechsler Intelligence Scale for Children 4th Edition (WISC-IV) (Wechsler 2003), a commonly used intelligence test in clinical practice. It includes 10 subtests and the total score (sum of all sub-tests, in the following referred to as Full developmental score) corresponds to the children's general intellectual ability. We also report data for four sub-scales: i) Verbal comprehension (based on sub-tests for vocabulary, information, and comprehension), ii) Perceptual reasoning (problem solving skill, block design, picture concepts, and matrix reasoning), iii) Working memory (digit span and arithmetic), and iv) Processing speed (coding and symbol search). To avoid potential bias when comparing with foreign culture norms, we used the WISC-IV raw scores, not the adjusted scales to a mean of 100, related to U.S. norms. The test materials and questionnaires were translated into Bengali and culturally adapted without changes in the underlying context. Testing was performed at the local health care facilities by four female psychologists who had undergone six weeks of training. They showed good inter-rater reliabilities with their trainer (Rahman et al., 2017b).

2.4. Covariates

Information on parental education (defined as the number of years at school; categorized as 0, 1–4, 5–9, ≥10 years) and maternal age, body weight, height, and smoking was collected during the MINIMat trial (Persson et al., 2012). None of the mothers reported smoking during pregnancy. A detailed history of socio-economic status (SES) was collected in early pregnancy and updated at 10 years of age. It included data on parental education, number of family members, assets owned by the family, imbalance between income and expenditure and quality of the roof, floor and walls of the house. An asset score (used as quintiles) was developed using principal component analysis. At the follow-up at 5 years of age, maternal IQ was evaluated using the Raven's colored and Progressive Matrices test (Hamadani et al., 2011), measuring non-verbal IQ in terms of abstract logical reasoning.

At the follow-up at 10 years, we gathered information on the number of children in the household, children's formal schooling (years), and the type of school they attended [public primary school, Madrasa (Islamic) school, NGO (non-profit private) school, and English medium (private) school]. Very few children did not attend school (n = 9) and, based on the developmental scoring by school group, these children were grouped together with those who attended religious schools (n = 161) and NGO schools (n = 39). The remaining two categories included children who attended ii) primary school (n = 1163) and iii) English medium school (n = 151). To assess the quality and quantity of stimulation and support of the children at home, we used a modified version of the Home Observation for Measurement of Environment (HOME) for middle childhood (6–10 years) (Caldwell and Bradley, 2003). Four research assistants were trained to interview mothers at the home visits. Ten percent of the interviews were supervised, and good inter-observer agreement was achieved. The children's height and weight were measured at the health care facilities after the developmental testing and converted into standardized z-scores for height-for-age (HAZ), weight-for-age (WAZ), and body mass index (BMI) for age (BAZ), using the WHO growth references (WHO 2006). According to the WHO standard, children with < -2 of HAZ or WAZ scores are considered stunted and underweight, respectively. The children's hemoglobin (Hb) concentrations in peripheral blood (finger prick) were measured by a HemoCue photometer (HemoCue AB, Ängelholm, Sweden).

2.5. Statistical methods

Statistical analyses were performed using the software package Stata 15 (StataCorp, TX, USA). P-values < 0.05 were considered statistically significant, but we also considered trends and consistency in the results. Bivariate associations between arsenic biomarkers (urinary arsenic at 5 and 10 years, hair arsenic at 10 years of age, and the mother's urinary and erythrocyte arsenic in pregnancy), outcomes (Full developmental score, Verbal Comprehension, Perceptual reasoning, Working memory, and Processing speed), and covariates were explored with Spearman correlation coefficients, Mann-Whitney *U* test, or Kruskall-Wallis test, depending on the type of data. We also examined the associations between exposures and the outcomes using scatter plots with a moving average Lowess curve, which indicated non-linear relationships of arsenic exposure with some of the cognitive abilities, even when using $\log_2$-transformed arsenic concentrations. Therefore, the different biomarkers of arsenic exposure were divided into quintiles (Q).

We then created multivariable-adjusted linear regression models examining the associations of mothers' and children's arsenic biomarkers with children's cognitive abilities at 10 years of age. The models were adjusted for covariates that were either *i*) selected a priori (gender, age at assessment, and tester of cognitive abilities), *ii*) correlated ($p < 0.05$) with both exposure (at any time) and outcomes (BAZ, family SES at 10 years, father's education, mother's education, mother's IQ, and level of home stimulation), or *iii*) that previously had been associated with the outcomes [school grade, type of school, number of children in the household, as well as urinary cadmium and water manganese (both $\log_2$-transformed) (Gustin et al., 2018; Rahman et al., 2017b)]. Mothers' education was highly correlated with mothers' IQ and SES, and therefore we included fathers' education in the regression models to avoid collinearity. In the first step of the analysis (Model 1), we adjusted for gender, age and testers, as we found that the psychologists scored somewhat different. In the second step (Model 2), we additionally adjusted for all potential confounders, i.e., BAZ, fathers' education, mothers' IQ, HOME, SES, number of children in the household, number of years at school and type of school, as well as urinary

cadmium and water manganese. As we previously observed gender-differences in arsenic toxicity (Broberg et al., 2014; Gardner et al., 2013; Hamadani et al., 2011), we also tested for a multiplicative interaction between gender and the different arsenic biomarkers in Model 2 and performed stratified analyses. In sensitivity analysis, we also included the supplementations provided to the mothers during pregnancy (6 groups).

To further compare the importance of the different exposure periods for the cognitive abilities at 10 years of age, we included the urinary arsenic concentrations (as quintiles) in early pregnancy and at 5 and 10 years in the same regression models. The variation inflation factor (vif) varied between 1.10 and 2.47 for the different quintiles in the different exposure measures, indicating acceptable multi-collinearity.

3. Results

3.1. Background characteristics

Background characteristics of the studied children and their families are shown in Table 1 by quintiles of child urinary arsenic at 10 years. The age range of the 1523 children assessed for arsenic exposure and cognitive abilities was narrow (8.8–10.1 years). Forty-two percent of the children were underweight (< -2 of WAZ) and 27% were stunted (< -2 of HAZ). The girls (47% of the children) were more underweight (46% with < -2 of WAZ) and stunted (30% with < -2 of HAZ) than the boys (41% and 25%, respectively). Children in the lowest quintile of urinary arsenic at 10 years of age were more likely to have higher socioeconomic status and more educated parents than children in the higher quintiles (Table 1). Children in the lowest quintile of urinary arsenic also had slightly lower concentrations of urinary cadmium and markedly higher concentrations of water manganese than children in the higher quintiles (r_S = 0.13 for urinary arsenic and cadmium, and r_S = -0.43 for urinary arsenic and water manganese, both p < 0.001). They also had higher raw scores of all cognitive abilities (Table 1). The overall test raw scores for all children and by gender are presented in Supplemental Table S1.

The overall median urinary arsenic concentration of the children at 5 and 10 years of age was 53 and 57 μg/L, respectively, with no significant gender difference (5 years: median 52 μg/L in girls and 53 μg/L in boys, p = 0.74; 10 years: median 54 μg/L in girls and 60 μg/L in boys, p = 0.54). The urinary concentrations of arsenic in their mothers in early pregnancy were generally higher, with a median value of 82 μg/L. Still, the children in the highest quintile of urinary arsenic at 10 years of age (median 265 μg/L) had higher median concentration than their mothers (median 193 μg/L in the highest quintile; Table 1), and those in quintiles 3–5 (median values 57, 104 and 265 μg/L,

Table 1
Characteristics, exposures and outcomes of the 1523 studied children by quintiles of their urinary arsenic concentrations at 10 years of age.

	Quintiles of child urinary arsenic at 10 years of age, μg/L[a], median (range)					
Characteristics[b]	Q1	Q2	Q3	Q4	Q5	
Median (range)	22.6 (7.3–29.9)	36.7 (30.0–45.5)	57.3 (45.6–73.1)	104 (73.4–162)	265 (163–940)	p[c]
Number of children	305	305	304	305	304	
Age at testing (years)	9.51 ± 0.11	9.50 ± 0.09	9.51 ± 0.09	9.52 ± 0.09	9.52 ± 0.08	0.021
Height (cm)	126.8 ± 5.9	126.2 ± 6.4	126.3 ± 5.9	126.6 ± 5.1	126.5 ± 5.9	0.868
Weight (kg)	23.8 ± 4.3	23.3 ± 4.0	23.3 ± 3.8	23.1 ± 3.1	23.2 ± 3.8	0.695
BMI (kg/m^2)	14.7 ± 2.0	14.6 ± 1.6	14.5 ± 1.6	14.4 ± 1.3	14.4 ± 1.78	0.463
Height-for-age Z-score	−1.39 ± 0.95	−1.47 ± 1.04	−1.46 ± 0.94	−1.41 ± 0.81	−1.43 ± 0.95	0.930
Weight-for-age Z-score	−1.63 ± 1.10	−1.74 ± 1.10	−1.76 ± 1.06	−1.79 ± 0.94	−1.79 ± 1.02	0.719
BMI-for-age Z-score	−1.17 ± 1.11	−1.24 ± 1.08	−1.29 ± 1.09	−1.37 ± 1.02	−1.36 ± 1.14	0.471
Number of siblings	2.9 ± 1.1	3.0 ± 1.1	3.0 ± 1.1	3.1 ± 1.1	3.0 ± 1.1	0.166
Socioeconomic status	−0.34 (-2.9–11.1)	−0.88 (-3.2–10.2)	−0.91 (-3.0–9.6)	−0.98 (–3.0–8.8)	−1.05 (-3.2–9.0)	< 0.001
Mothers' education (years)	6.1 ± 4.0	5.1 ± 3.8	4.8 ± 3.6	4.7 ± 3.5	5.0 ± 3.5	< 0.001
Fathers' education (years)	6.7 ± 4.6	5.2 ± 4.4	5.2 ± 4.2	4.7 ± 4.0	5.2 ± 4.1	< 0.001
HOME	27.8 ± 5.2	26.8 ± 5.1	26.9 ± 4.7	26.6 ± 4.7	26.7 ± 5.0	0.036
Number of years at school	4.0 ± 0.20	3.9 ± 0.30	4.0 ± 0.20	3.9 ± 0.26	4.0 ± 0.27	0.982
Type of school (%)[d]	11.1/ 77.8/11.1	12.6/77.8/ 9.6	15.8/ 76.5/7.7	16.6/ 73.6/9.8	12.9/ 76.0/11.1	0.223
Hemoglobin (g/L)[e]	118 ± 12.2	119 ± 10.8	118 ± 11.9	119 ± 10.7	119 ± 10.2	0.536
Hair arsenic (ng/g)[f]	246 (63–3527)	308 (73–3120)	396 (99–3297)	643 (93–3590)	1693 (141–8724)	< 0.001
Hair selenium (ng/g)[f]	492 ± 83.5	494 ± 86.6	489 ± 83.7	483 ± 80.4	477 ± 83.9	0.110
Urinary cadmium (μg/L)[a]	0.21 (0.04–0.99)	0.22 (0.04–2.6)	0.25 (0.04–2.5)	0.26 (0.02–1.7)	0.26 (0.04–2.3)	< 0.001
Urinary lead (μg/L)[a]	1.5 (0.38–11.5)	1.7 (0.26–12.0)	1.5 (0.16–16.0)	1.6 (0.06–8.9)	1.5 (0.23–27.7)	0.456
Water arsenic (μg/L)	0.32 (0.01–299)	0.56 (0.01–333)	1.58 (0.01–510)	23.9 (0.01–482)	193 (0.06–834)	< 0.001
Water manganese (μg/L)	1240 (0.4–6984)	891 (0.1–8680)	419 (0.5–7266)	125 (0.3–5563)	83 (0.2–5639)	< 0.001
Urinary arsenic at 5 years (μg/L)[a,g]	32 (6.8–426)	42 (9.7–669)	47 (12–813)	74 (15–601)	183 (17–1016)	< 0.001
Maternal urinary arsenic GW8 (μg/L)[a,g]	42 (3.2–831)	52 (3.2–1275)	68 (7.4–1122)	127 (7.0–1287)	193 (16–1184)	< 0.001
Maternal erythrocyte arsenic GW14 (μg/L)[a,g]	2.4 (0.38–29.7)	3.1 (0.15–86.6)	4.1 (0.57–56.6)	6.4 (0.73–55.3)	10.0 (1.0–67.2)	< 0.001
Full developmental score[h]	141 ± 34	135 ± 33	126 ± 34	127 ± 31	132 ± 31	< 0.001
Verbal comprehension[h]	40 ± 11	38 ± 11	35 ± 10	36 ± 9.5	36 ± 9.9	< 0.001
Perceptional reasoning[h]	35 ± 13	32 ± 11	30 ± 11	30 ± 11	32 ± 11	< 0.001
Working memory[h]	31 ± 6.0	30 ± 5.7	29 ± 6.6	29 ± 6.3	30 ± 5.9	< 0.001
Processing speed[h]	36 ± 12	35 ± 12	33 ± 12	32 ± 11	35 ± 11	< 0.001

Abbreviations: BMI, body mass index; HOME, Home Observations for Measurement of Environment; GW, gestational week.

[a] Adjusted for specific gravity to mean of 1.012.

[b] Mean ± standard deviation or median (range).

[c] Kruskal-Wallis (continuous variables) or Chi^2 test (categorical variables).

[d] 1) No school, religious schools and NGO schools (n = 200), 2) primary school (n = 1114) and 3) English medium school (n = 143).

[e] Only available for 1498.

[f] Only available for 1446.

[g] Urinary arsenic at 5 years was available for 1477, maternal urinary arsenic at GW8 for 1467, and maternal erythrocyte arsenic at GW14 for 1439.

[h] WISC-IV raw scores.

Table 2
Linear regression analysis of associations between urinary arsenic (quintiles; μg/L) of the children or their mothers during early pregnancy and the cognitive abilities at 10 years of age. Each model includes urinary arsenic at one time point only.

Exposure time point	Quintiles of urinary arsenic						
	Q1 **B (95% CI)**	Q2 **B (95% CI)**	Q3 **B (95% CI)**	Q4 **B (95% CI)**	Q5 **B (95% CI)**	p_{trend}	p_{int}
Children 10 years							
n	305	305	304	305	304		
Median (range), μg/L	22.6 (7.3–29.9)	36.7 (30.0–45.5)	57.3 (45.6–73.1)	104 (73.4–162)	265 (163–940)		
Full developmental score							
Model 1[a]	Reference	−7.44 (−12.6; −2.31)	−15.7 (−20.9; −10.6)	−15.2 (−20.4; −10.1)	−9.46 (−14.6; −4.33)		
Model 2[b]	Reference	−1.63 (−5.62; 2.36)	−7.23 (−11.3; −3.18)	−6.37 (−10.5; −2.22)	−2.71 (−6.96; 1.54)	0.042	0.325
Verbal comprehension							
Model 1[a]	Reference	−2.34 (−3.96; −0.72)	−5.09 (−6.70; −3.47)	−4.31 (−5.92; −2.69)	−3.68 (−5.30; −2.06)		
Model 2[b]	Reference	−0.56 (−1.87; 0.75)	−2.58 (−3.91; −1.25)	−1.64 (−3.91; −1.25)	−1.60 (−3.00; −0.20)	0.009	0.660
Perceptual reasoning							
Model 1[a]	Reference	−2.85 (−4.63; −1.07)	−5.00 (−6.78; −3.22)	−4.84 (−6.62; −3.06)	−3.36 (−5.14; −1.58)		
Model 2[b]	Reference	−1.25 (−2.81; 0.31)	−2.62 (−4.21; −1.03)	−2.44 (−4.07; −0.82)	−1.45 (−3.12; 0.21)	0.035	0.747
Working memory							
Model 1[a]	Reference	−1.23 (−2.18; −0.28)	−2.25 (−3.20; −1.29)	−2.00 (−2.95; −1.05)	−0.96 (−1.91; −0.00)		
Model 2[b]	Reference	−0.40 (−1.21; 0.42)	−1.02 (−1.85; −0.19)	−0.68 (−1.53; 0.17)	−0.04 (−0.91; 0.83)	0.725	0.258
Processing speed							
Model 1[a]	Reference	−1.02 (−2.85; 0.82)	−3.40 (−5.24; −1.57)	−4.09 (−5.92; −2.25)	−1.46 (−3.30; 0.37)		
Model 2[b]	Reference	0.57 (−1.01; 2.16)	−1.02 (−2.63; 0.59)	−1.61 (−3.26; 0.04)	0.38 (−1.31; 2.07)	0.482	0.101
Children 5 years							
n	296	295	296	295	295		
Median (range), μg/L	21 (6–27)	34 (28–41)	53 (42–69)	100 (70–149)	236 (150–1020)		
Full developmental score							
Model 1[a]	Reference	−2.90 (−8.16; 2.37)	−7.62 (−8.16; −2.37)	−9.35 (−14.6; −4.09)	−4.61 (−9.87; 2.37)		
Model 2[b]	Reference	−1.53 (−5.63; 2.56)	−3.30 (−7.41; 0.81)	−2.57 (−6.78; 1.65)	0.59 (−3.67; 4.86)	0.973	0.079
Verbal comprehension							
Model 1[a]	Reference	−0.57 (−2.23; 1.10)	−1.52 (−3.20; 0.15)	−2.68 (−4.34; −1.01)	−1.46 (−3.13; 0.20)		
Model 2[b]	Reference	−0.04 (−1.39; 1.31)	−0.16 (−1.52; 1.19)	−0.60 (−1.99; 0.79)	0.30 (−1.11; 1.70)	0.971	0.045
Perceptual reasoning							
Model 1[a]	Reference	−0.72 (−2.53; 1.10)	−2.41 (−4.23; −0.59)	−2.96 (−4.77; −1.14)	−1.72 (−3.53; 0.10)		
Model 2[b]	Reference	−0.29 (−1.89; 1.31)	−1.17 (−2.78; 0.43)	−1.06 (−2.70; 0.59)	−0.26 (−1.93; 1.40)	0.497	0.313
Working memory							
Model 1[a]	Reference	−0.17 (−1.14; 0.80)	−0.74 (−1.72; 0.24)	−0.94 (−1.91; 0.03)	−0.05 (−1.02; 0.92)		
Model 2[b]	Reference	−0.13 (−0.96; 0.71)	−0.21 (−1.05; 0.63)	−0.03 (−0.89; 0.83)	0.54 (−0.33; 1.41)	0.239	0.502
Processing speed							
Model 1[a]	Reference	−1.44 (−3.32; 0.43)	−2.94 (−4.82; −1.06)	−2.78 (−4.65; −0.90)	−1.38 (−3.25; 0.50)		
Model 2[b]	Reference	−1.07 (−2.69; 0.55)	−1.76 (−3.39; −0.13)	−0.88 (−2.55; 0.78)	0.02 (−1.66; 1.71)	0.905	0.190
Mothers gestational week 8							
n	294	293	294	293	293		
Median (range)	23.8 (3.2–32.4)	43.5 (32.5–58.8)	83.5 (58.9–122)	174 (122–246)	381 (247–1287)		
Full developmental score							
Model 1[a]	Reference	−5.33 (−10.6; −0.04)	−9.04 (−14.3; −3.73)	−8.98 (−14.3; −3.63)	−11.0 (−16.3; −5.71)		
Model 2[b]	Reference	−4.52 (−8.61; −0.43)	−5.91 (−10.0; −1.77)	−5.98 (−10.2; −1.77)	−3.41 (−7.60; 0.77)	0.094	0.021
Verbal comprehension							
Model 1[a]	Reference	−2.15 (−3.83; −0.48)	−2.55 (−4.23; −0.87)	−2.90 (−4.59; −1.21)	−3.05 (−4.73; −1.37)		
Model 2[b]	Reference	−1.90 (−3.24; −0.56)	−1.50 (−2.86; −0.15)	−1.89 (−3.27; −0.50)	−0.65 (−2.02; 0.73)	0.430	0.164
Perceptual reasoning							
Model 1[a]	Reference	−0.00 (−1.83; 1.82)	−2.31 (−4.14; −0.47)	−2.65 (−4.50; −0.80)	−3.51 (−5.35; −1.68)		
Model 2[b]	Reference	0.23 (−1.37; 1.83)	−1.46 (−3.08; 0.15)	−1.79 (−3.44; −0.15)	−1.48 (−3.12; 0.15)	0.010	0.010
Working memory							
Model 1[a]	Reference	−0.79 (−1.77; 0.18)	−0.80 (−1.78; 0.17)	−0.73 (−1.71; 0.26)	−1.32 (−2.30; −0.35)		
Model 2[b]	Reference	−0.71 (−1.54; 0.12)	−0.38 (−1.23; 0.46)	−0.34 (−1.20; 0.52)	−0.21 (−1.06; 0.64)	0.939	0.094
Processing speed							
Model 1[a]	Reference	−2.39 (−4.26; −0.51)	−3.38 (−5.26; −1.50)	−2.70 (−4.60; −0.81)	−3.13 (−5.01; −1.25)		
Model 2[b]	Reference	−2.15 (−3.76; −0.53)	−2.55 (−4.18; −0.92)	−1.97 (−3.63; −0.30)	−1.07 (−2.72; 0.58)	0.315	0.409

B is the unstandardized regression coefficient.

[a] Model 1: Adjusted for child gender, age at testing and tester. In relation to the concurrent urinary arsenic at 10 years this model included 1532 children, for urinary arsenic at 5 years the corresponding number of children were 1501, and for the mother's urinary arsenic during pregnancy it was 1467.

[b] Model 2: Further adjusted for child BMI-for-age, type of school (no school, religious school, NGO or primary school, or English medium school), school grade, number of children in the household, family SES (quintiles), father's level of education (0, 1–5, 5–10, ≥10 years), motheŕs IQ, level of home stimulation, child urinary cadmium (μg/L, log2 transformed) and water manganese (μg/L, log2 transformed; 10 years). In relation to the concurrent urinary arsenic at 10 years this model included 1532 children, for urinary arsenic at 5 years the corresponding number of children were 1471, and for the mother's urinary arsenic during pregnancy it was 1460.

respectively) had 21–45% higher median concentrations than at 5 years (47, 74 and 183 μg/L). Arsenic concentrations in child urine showed a significant correlation with arsenic in hair (r_S = 0.59; p < 0.001). Similarly, arsenic concentrations in erythrocytes at GW14 correlated with arsenic concentrations in urine, collected a few weeks earlier, around GW8 (r_S = 0.65; p < 0.001).

3.2. Arsenic and children's cognitive abilities – cross-sectional analyses

In the regression analyses adjusted for child sex, age and tester (Model 1; Table 2), children in quintiles 2–5 of urinary arsenic at 10 years had significantly lower Full developmental scores than the children in the lowest quintile. After additional adjustments (Model 2, Table 2), the estimates were considerably weakened (more than halved), and only those in quintiles 3–4 remained statistically significant, with 6–7 points lower scores compared to the first quintile (p for trend 0.042). The arsenic-associated decrease in the Full developmental scores seemed to be explained mainly by the associations with Verbal comprehension and Perceptual reasoning (Table 2). Again, the estimates in the fully adjusted model (Model 2) were less than half of those in Model 1. For both outcomes, there were significantly decreasing trends across quintiles of arsenic exposure, with 1.5–2.7 points lower scores in quintiles 3–5 of urinary arsenic, compared to the first quintile (p for trend was 0.009 and 0.035, respectively). Arsenic in urine was not associated with Working memory. Further adjusting Model 2 in Table 2 for the different supplementations during pregnancy (6 groups) did not change the results (estimates of Full developmental score for Q2-Q5: −1.49, −7.16, −6.27, −2.58).

The interaction term between children's urinary arsenic and gender in relation to the Full developmental scores and its sub-scales was not significant (p > 0.10; Table 2), and after stratifying by gender, the inverse associations were not very different between girls and boys (Fig. 1; Supplemental Table S2). For the Full developmental scores, girls in the third to fifth quintiles had about 6–7 points lower score than girls in the lowest quintile (p for trend 0.014). Similar estimates were observed for boys in the third and fourth quintiles, however, the estimate in the fifth quintile was close to null (p for trend 0.63). This tendency of a U-shaped association for the boys was not as clear for the sub-scales Verbal comprehension and Perceptual reasoning. To note, the arsenic concentrations in the fifth quintile were quite similar for boys and girls (boys 310 ± 145 μg/L, girls 313 ± 140 μg/L), as were the concentrations in the first (reference) quintile (22.5 ± 4.9 for boys and 22.7 ± 5.2 for girls).

The results of the regression analyses with children's hair arsenic concentrations (Supplemental Table S3) were very similar to those with urinary arsenic, both for the Full developmental scores and the sub-scales. The interaction term (gender × hair arsenic) for the Full developmental score was not statistically significant (p > 0.05).

3.3. Arsenic and children's cognitive abilities – Prospective analyses

Evaluation of cognitive abilities at 10 years in relation to the urinary arsenic concentrations at 5 years showed much weaker associations than in the cross-sectional analyses (Table 2). The multivariable-adjusted regression analysis showed about 3 points lower Full developmental scores in quintiles 3–4, compared to the first quintile, although not statistically significant. The interaction term for gender × urinary arsenic was close to significant for Full developmental scores (p = 0.079), but not significant for the other outcomes (Table 2). Stratifying by gender (Fig. 1; Supplemental Table S2) showed significantly inverse associations for Full developmental scores, Verbal comprehension and Processing speed in the girls, while there were no significant associations with urinary arsenic at 5 years in the boys.

Concerning the associations between maternal urinary arsenic in early pregnancy and the cognitive abilities, the differences between Model 1 (adjusted for age, sex, and tester) and the fully adjusted Model 2 were smaller than in the cross-sectional analyses (Table 2). In the fully adjusted regression analysis, maternal urinary arsenic was significantly inversely associated with Full developmental scores, Verbal comprehension, Perceptual reasoning, and Processing speed (Table 2). The Full developmental scores were on average 5–6 points lower in quintiles 2–4 than in quintile 1, while those in the sub-tests were 1.5–2.5 points lower in quintiles 2–4 (quintiles 3–5 for Perceptual reasoning), compared to the first quintile. The interaction term for gender × maternal urinary arsenic was significant for Full developmental score and Perceptual reasoning (p values 0.021 and 0.010, respectively; Table 2), and stratifying by gender (Fig. 1; Supplemental Table S2) showed stronger associations with Full developmental scores, Verbal comprehension, Perceptual reasoning and Processing speed in girls (all statistically significant in at least two quintiles) than in boys (no significant inverse associations). In the girls, the Full developmental scores decreased already in the second quintile, and the decrease appeared to be quite stable across the four quintiles (average −8.6 points). Further adjusting Model 2 in Table 2 for the different supplementations during pregnancy (6 groups) did not change the results (estimates of Full developmental score for Q2-Q5: −4.54, −5.79, −6.06, −3.41).

The models using erythrocyte arsenic in GW14 as exposure measure showed overall similar results as those based on urinary arsenic in GW 8, but the associations were slightly weaker (Supplemental Table S4). The estimate for Full developmental score in the fourth quintile was −5.11 (95% CI: −9.41; −0.80), that for Verbal comprehension −1.91 (95% CI: −3.34; −0.497), and that for Perceptual reasoning −1.85 (95% CI: −3.53; −0.17), compared to the first quintile. The interaction term for gender × maternal erythrocyte arsenic was not statistically significant for any of the outcomes (p values > 0.1), but in line with the urine-based models, the gender-stratified analyses showed generally stronger associations for girls than for boys (except for Perceptual

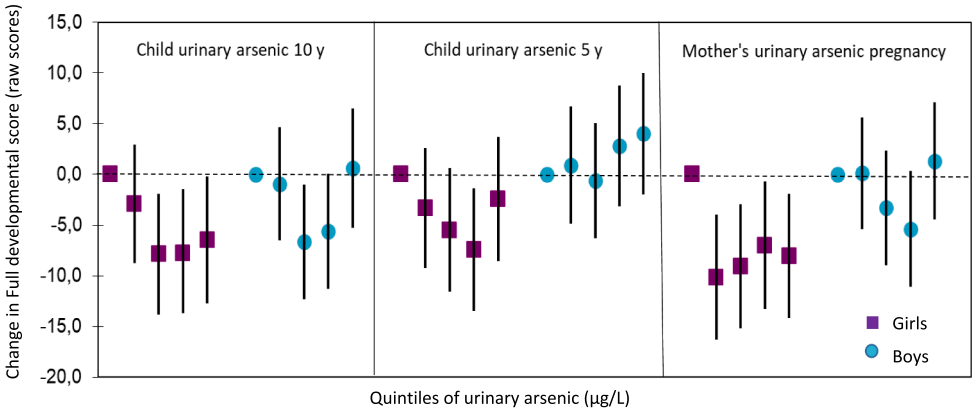

Fig. 1. Multivariable-adjusted associations of urinary arsenic (quintiles; μg/L) of the children at 10 and 5 years of age and their mothers during early pregnancy with children's Full developmental scores (raw scores) at 10 years of age by gender. Models were adjusted for age at testing, tester, child BMI-for-age, type of school (no school, religious school, NGO or primary school, or English medium school), school grade, number of children in the household, family SES (quintiles), father's level of education (0, 1–5, 5–10, ≥10 years), mother's IQ, level of home stimulation, child urinary cadmium (μg/L, $\log_2$ transformed) and water manganese (μg/L, $\log_2$ transformed; 10 years).

Table 3
Linear regression analysis of associations between combined exposure at 10 years, 5 years, and prenatally (quintiles of urinary arsenic at 10 years, 5 years and the mothers in early pregnancy included in the same model). The models are based on data for 1412 children, out of which 675 were girls and 737 were boys.

Outcomes with the combined exposures	Quintiles of urinary arsenic					
	Q1 B (95%CI)	Q2 B (95%CI)	Q3 B (95%CI)	Q4 B (95%CI)	Q5 B (95%CI)	p_{trend}
Full developmental score						
Urinary arsenic at 10 years						
All children[a]	Reference	−2.12 (−6.34; 2.09)	−7.20 (−11.5; −2.89)	−6.22 (−10.8; −1.64)	−3.76 (−8.89; 1.37)	0.044
Girls[b]	Reference	−2.72 (−8.83; 3.38)	−6.36 (−12.6; −0.08)	−7.16 (−13.8; −0.50)	−7.53 (−15.0; −0.10)	0.030
Boys[b]	Reference	−2.09 (−8.03; 3.85)	−7.19 (−13.2; −1.16)	−5.90 (−12.3; 0.53)	−0.86 (−8.11; 6.39)	0.388
Urinary arsenic at 5 years						
All children[a]	Reference	−0.48 (−4.70; 3.75)	−1.17 (−5.49; 3.15)	0.26 (−4.30; 4.82)	2.71 (−2.41; 7.83)	0.166
Girls[b]	Reference	−0.71 (−6.87; 5.45)	−1.70 (−8.19; 4.79)	−3.54 (−10.1; 2.99)	3.39 (−4.05; 10.8)	0.598
Boys[b]	Reference	0.55 (−5.37; 6.46)	0.45 (−5.48; 6.38)	5.05 (−1.42; 11.5)	2.79 (−4.37; 9.95)	0.118
Urinary arsenic of mothers at GW8						
All children[a]	Reference	−3.58 (−7.79; 0.63)	−4.59 (−8.90; −0.28)	−5.04 (−9.54; −0.53)	−2.91 (−7.56; 1.75)	0.268
Girls[b]	Reference	−9.40 (−15.8; −3.04)	−7.92 (−14.3; −1.50)	−5.82 (−12.5; 0.84)	−7.04 (−13.9; −0.23)	0.283
Boys[b]	Reference	1.26 (−4.41; 6.92)	−2.42 (−8.33; 3.49)	−5.21 (−11.4; 1.00)	1.04 (−5.49; 7.57)	0.701
Verbal comprehension						
Urinary arsenic at 10 years						
All children[a]	Reference	−0.78 (−2.17; 0.60)	−2.62 (−4.04; −1.20)	−1.68 (−3.18; −0.17)	−2.24 (−3.92; −0.55)	0.004
Girls[b]	Reference	−0.75 (−2.70; 1.21)	−2.15 (−4.17; −0.14)	−1.33 (−3.46; 0.80)	−2.81 (−5.19; −0.43)	0.025
Boys[b]	Reference	−1.07 (−3.07; 0.93)	−3.10 (−5.14; −1.07)	−2.21 (−4.37; −0.04)	−2.02 (−4.47; 0.42)	0.038
Urinary arsenic at 5 years						
All children[a]	Reference	0.36 (−1.03; 1.75)	0.53 (−0.89; 1.95)	0.34 (−1.15; 1.84)	1.20 (−0.49; 2.88)	0.135
Girls[b]	Reference	−0.71 (−2.68; 1.26)	−0.14 (−2.22; 1.95)	−0.74 (−2.83; 1.35)	0.84 (−1.54; 3.23)	0.552
Boys[b]	Reference	1.57 (−0.43; 3.56)	1.37 (−0.63; 3.37)	1.69 (−0.49; 3.87)	1.73 (−0.68; 4.14)	0.102
Urinary arsenic of mothers GW8						
All children[a]	Reference	−1.64 (−3.03; −0.26)	−1.17 (−2.59; 0.24)	−1.49 (−2.97; −0.004)	−0.16 (−1.69; 1.37)	0.955
Girls[b]	Reference	−3.13 (−5.17; −1.09)	−2.09 (−4.14; −0.03)	−2.22 (−4.36; −0.09)	−1.70 (−3.89; 0.48)	0.493
Boys[b]	Reference	−0.54 (−2.45; 1.37)	−0.29 (−2.29; 1.70)	−0.97 (−3.07; 1.12)	1.25 (−0.95; 3.46)	0.425
Perceptual reasoning						
Urinary arsenic at 10 years						
All children[a]	Reference	−1.52 (−3.16; 0.13)	−2.71 (−4.39; −1.03)	−2.26 (−4.05; −0.46)	−1.42 (−3.42; 0.59)	0.121
Girls[b]	Reference	−1.32 (−3.62; 0.99)	−1.50 (−3.88; 0.87)	−1.61 (−4.12; 0.90)	−1.49 (−4.29; 1.32)	0.363
Boys[b]	Reference	−1.90 (−4.29; 0.48)	−3.40 (−5.82; −0.98)	−2.97 (−5.55; −0.39)	−1.47 (−4.38; 1.44)	0.162
Urinary arsenic at 5 years						
All children[a]	Reference	−0.13 (−1.78 1.52)	−0.76 (−2.45; 0.93)	−0.22 (−2.01; 1.56)	0.57 (−1.43; 2.57)	0.505
Girls[b]	Reference	0.22 (−2.10; 2.55)	−1.11 (−3.56; 1.34)	−1.24 (−3.71; 1.22)	0.88 (−1.93; 3.69)	0.944
Boys[b]	Reference	−0.03 (−2.40; 2.35)	−0.07 (−2.45; 2.31)	1.31 (−1.29; 3.90)	0.60 (−2.27; 3.48)	0.301
Urinary arsenic of mothers at GW8						
All children[a]	Reference	0.47 (−1.17; 2.12)	−0.98 (−2.66; 0.71)	−1.46 (−3.22; 0.30)	−1.25 (−3.07; 0.57)	0.074
Girls[b]	Reference	−2.27 (−4.67; 0.14)	−2.17 (−4.59; 0.26)	−2.02 (−4.54; 0.49)	−3.10 (−5.67; −0.52)	0.074
Boys[b]	Reference	2.70 (0.43; 4.97)	−0.40 (−2.77; 1.97)	−1.44 (−3.94; 1.05)	0.39 (−2.23; 3.01)	0.435
Working memory						
Urinary arsenic at 10 years						
All children[a]	Reference	−0.52 (−1.38; 0.34)	−1.11 (−1.99; −0.23)	−0.73 (−1.66; 0.21)	−0.45 (−1.49; 0.60)	0.322
Girls[b]	Reference	−0.32 (−1.53; 0.89)	−1.10 (−2.34; 0.15)	−0.52 (−1.84; 0.80)	−1.02 (−2.49; 0.46)	0.174
Boys[b]	Reference	−0.78 (−2.03; 0.46)	−1.05 (−2.32; 0.21	−0.93 (−2.28; 0.41)	0.08 (−1.44; 1.59)	0.931
Urinary arsenic at 5 years						
All children[a]	Reference	−0.06 (−0.92; 0.81)	0.003(−0.88; 0.88)	0.21 (−0.72; 1.14)	0.66 (−0.38; 1.71)	0.117
Girls[b]	Reference	0.41 (−0.81; 1.64)	0.15 (−1.14; 1.43)	−0.18 (−1.48;1.11)	1.06 (−0.42; 2.54)	0.328
Boys[b]	Reference	−0.45 (−1.69; 0.79)	−0.05 (−1.29; 1.19)	0.70 (−0.66; 2.06)	0.32 (−1.18; 1.82)	0.195
Urinary arsenic of mothers at GW8						
All children[a]	Reference	−0.64 (−1.50; 0.22)	−0.30 (−1.18; 0.58)	−0.41 (−1.33; 0.50)	−0.35 (−1.30; 0.60)	0.802
Girls[b]	Reference	−1.46 (−2.73; −0.20)	−0.35 (−1.62; 0.93)	−0.15 (−1.47; 1.17)	−0.70 (−2.06; 0.65)	0.935
Boys[b]	Reference	0.21 (−0.98; 1.40)	−0.27 (−1.51; 0.97)	−0.65 (−1.95; 0.65)	0.10 (−1.27; 1.47)	0.809
Processing speed						
Urinary arsenic at 10 years						
All children[a]	Reference	0.69 (−0.97; 2.35)	−0.76 (−2.47; 0.94)	−1.56 (−3.37; 0.25)	0.34 (−1.68; 2.37)	0.506
Girls[b]	Reference	−0.34 (−2.85; 2.17)	−1.61 (−4.19; 0.98)	−3.69 (−6.43; −0.96)	−2.21 (−5.26; 0.85)	0.040
Boys[b]	Reference	1.66 (−0.61; 3.94)	0.36 (−1.95; 2.67)	0.21 (−2.25; 2.67)	2.55 (−0.22; 5.33)	0.276
Urinary arsenic at 5 years						
All children[a]	Reference	−0.65 (−2.32; 1.02)	−0.94 (−2.65; 0.76)	−0.07 (−1.87; 1.73)	0.28 (−1.74; 2.30)	0.423
Girls[b]	Reference	−0.64 (−3.17; 1.89)	−0.59 (−3.26; 2.08)	−1.37 (−4.05; 1.31)	0.61 (−2.45; 3.67)	0.776
Boys[b]	Reference	−0.55 (−2.81; 1.72)	−0.80 (−3.07; 1.47)	1.36 (−1.12; 3.83)	0.14 (−2.60; 2.88)	0.390

(*continued on next page*)

Table 3 (*continued*)

Outcomes with the combined exposures	Quintiles of urinary arsenic					
	Q1 B (95%CI)	Q2 B (95%CI)	Q3 B (95%CI)	Q4 B (95%CI)	Q5 B (95%CI)	p_{trend}
Urinary arsenic of mothers at GW8						
All children[a]	Reference	−1.77 (−3.44; −0.11)	−2.14 (−3.84; −0.44)	−1.68 (−3.46; 0.10)	−1.14 (−2.98; 0.70)	0.340
Girls[b]	Reference	−2.54 (−5.15; 0.08)	−3.31 (−5.95; −0.67)	−1.42 (−4.16; 1.32)	−1.54 (−4.34; 1.26)	0.627
Boys[b]	Reference	−1.11 (−3.28; 1.06)	−1.46 (−3.72; 0.81)	−2.14 (−4.52; 0.23)	−0.70 (−3.20; 1.80)	0.452

B is the unstandardized regression coefficient.

[a] Adjusted for child gender, age at testing, tester, child BMI-for-age, type of school (no school, religious school, NGO or primary school, or English medium school), school grade, number of children in the household, family SES (quintiles), father's level of education (0, 1–5, 5–10, ≥10 years), motheŕs IQ, level of home stimulation, child urinary cadmium (μg/L, log2 transformed) and water manganese (μg/L, log2 transformed; 10 years).

[b] Adjusted as defined above but excluding child gender.

reasoning; Supplemental Material Table S4).

Maternal urinary arsenic in late pregnancy (GW 30 on average) showed markedly weaker associations with cognitive abilities (Supplemental Material Table S5) compared to those based on early gestational urinary arsenic, even though the Spearman correlation between the two measures was 0.62 ($p < 0.001$).

3.4. Combined prenatal and childhood arsenic exposure

Entering both early prenatal and childhood (5 and 10 years) arsenic exposures based on urinary arsenic (quintiles) in the same models (Table 3, Model 2 only) revealed very similar associations between concurrent exposure at 10 years of age and cognitive abilities, as in the cross-sectional analyses. Thus, a statistically significant decrease of the estimates with increasing arsenic exposure (quintiles 3–4) was found for Full developmental score, Verbal comprehension, and Perceptual reasoning. Stratifying by gender showed quite similar estimates for girls and boys in relation to the exposure measures at 10 years, except for the fifth quintile where the estimate for Full developmental score was −7.5 for girls and close to null for boys.

In this combined exposure model, the 5-year exposure was not associated with any of the cognitive ability measures for all children (Table 3). The inverse associations with early prenatal arsenic exposure were slightly weakened after adjusting for both childhood exposure measures, compared to the single-exposure model. However, the estimate remained statistically significant for all the outcomes that were significant in the single-exposure models (all but Working memory), and still only in girls (Table 3). Again, the estimates based on early prenatal exposure decreased already in the second quintiles.

4. Discussion

This unique, large, longitudinal cohort study indicates that exposure to arsenic, both early prenatally and during childhood, is associated with lower cognitive abilities at 10 years of age. However, the arsenic-related decrease in cognitive abilities in the rural Bangladeshi children was rather modest, considering the very high exposure through drinking water in many of the families (range of children's urinary arsenic 7.3–940 μg/L). Nonetheless, the main decrease in cognitive abilities appeared at rather low exposure levels. The third and fourth quintiles of urinary arsenic at 10 years (range 46–73 and 73–162 μg/L, respectively) were associated with a decrease in the Full developmental scores of 6–7 points (raw scores), compared to the reference quintile of 7–30 μg/L, which mainly represents exposure through the rice-based diet (Kippler et al., 2016). This decrease corresponds to about 0.2 SD of the Full developmental scores (mean 132 ± 33). Also, the early prenatal exposure showed significant inverse associations, but mainly in girls, in whom the estimate for Full developmental scores decreased already in the second quintile (32–59 μg/L). Concerning the sub-scales, the scores of Verbal comprehension and Perceptual reasoning decreased by about 2 points (corresponding to about 0.2 SD) with increasing concurrent or prenatal exposure, while the scores of Processing speed decreased mainly in relation to the prenatal exposure (in girls). Only the results of the Working memory sub-test, which measures abilities like attention and mental control, showed no association with arsenic exposure at any time point.

The found cross-sectional associations based on child urinary arsenic at 10 years of age were supported by the corresponding associations based on hair arsenic concentrations, which represent arsenic exposure during the previous few months (Skroder et al., 2017b). The fairly strong correlation between arsenic in urine and hair ($r_S = 0.59$), despite the different time periods that they reflect (previous few days for arsenic in urine), was likely a result of the continuous arsenic exposure through drinking water and food. Although a short-term exposure biomarker like urinary arsenic could be expected to vary depending on the daily activities (with different water sources), the associations with cognitive abilities were quite consistent for urinary and hair arsenic. Similarly, the associations of maternal urinary arsenic in GW 8 with the measures of children's cognitive function were supported by models based on arsenic concentrations in blood (erythrocyte fraction), collected one and a half month later in pregnancy (on average in GW14). The somewhat weaker associations with arsenic concentrations in erythrocyte may, at least partly, be explained by the rapid increase in the methylation efficiency of arsenic, converting inorganic arsenic and the initial metabolite MMA to the less toxic DMA. This change in the biotransformation of arsenic takes place very early in pregnancy (Gardner et al., 2011b). In line with this, the associations based on urinary arsenic at GW 30 were even weaker, and generally not statistically significant. We did not evaluate children's cognitive abilities against arsenic concentrations in the drinking water, as we previously reported that there is a substantial exposure to arsenic also through food (Gardner et al., 2011a; Kippler et al., 2016). In addition, we only had water samples from the homes, not from the schools and other places where the children spent their days. Therefore, we used biomarkers of exposure, reflecting the actual ingested amount of arsenic from all sources.

The general concept that the brain is particularly vulnerable to toxic insult during early development (Grandjean and Landrigan 2014) is supported by the present findings, as both the concurrent exposure to arsenic and that during early fetal development appeared to influence the cognitive abilities at 10 years of age. In our previous study of the children's cognitive abilities at 5 years of age, arsenic exposure was inversely associated with Verbal IQ, but not with Performance IQ, which was based on the Perceptual Reasoning sub-tests Block Design, Matrix Reasoning, and Picture Completion (Hamadani et al., 2011). At 10 years of age, arsenic exposure was inversely associated with both Verbal Comprehension and Perceptual reasoning, indicating a more widespread impact on cognitive abilities over time, or that the tests of cognitive abilities are more sensitive at 10 years than that at 5 years. Previous studies on arsenic and cognitive function in children in

Bangladesh, India, Mexico, southern Europe, and USA are not consistent as to the specific cognitive targets of arsenic (Rodrigues et al., 2016; Rosado et al., 2007; Signes-Pastor et al., 2019; Wasserman et al., 2014; Wasserman et al., 2011; von Ehrenstein et al., 2007).

In contrast to the found cross-sectional associations at 10 years in the present study, the associations with prenatal arsenic were restricted to exposure in early gestation (not late gestation), appeared at lower exposure levels (already in quintile 2), and mainly in the girls. Also, the associations based on early prenatal exposure were less influenced by adjustment for covariates, compared to the cross-sectional associations. Taken together, this might indicate different toxic mechanisms of prenatal and childhood arsenic exposure. It is well known that arsenic easily passes the placenta to the fetus (Concha et al., 1998), and in experimental studies on mice, arsenic exposure in early gestation was found to cause specific accumulation in the embryonic neuroepithelium, which may lead to toxicity (Lindgren et al., 1984). For instance, arsenic may interfere with the extensive fitness-dependent programmed death of many of the neurons formed during embryonic development (Wang et al., 2019), as arsenic is known to induce neuronal apoptosis (Chattopadhyay et al., 2002; Pandey et al., 2017). Other potential mechanisms include epigenetic modifications (Winterbottom et al., 2019). We previously found that arsenic exposure (maternal urinary arsenic) in early gestation was associated with alterations in DNA methylation in cord blood in a sex-specific manner (Broberg et al., 2014). Although the epigenetic effects were less pronounced in newborn girls than in boys, they were mainly related to fetal development. The associations based on arsenic exposure in late gestation were much weaker.

Given the multidimensional and compelling toxicity of arsenic (EFSA, 2014; IARC, 2012), the found modest associations with cognitive abilities in children are surprising. Nevertheless, the finding that prenatal arsenic exposure appeared to influence the test results at 10 years of age suggests that effects induced by arsenic during early fetal development are irreversible. The observed much stronger inverse associations of cognitive abilities with the concurrent exposure at 10 years of age than with the exposure 5 years earlier might indicate an aggravation of the effects with time of continued childhood exposure. Thus, it is essential to follow-up the arsenic-exposed children in the different cohorts, even those with modest exposure. Also, the importance of continued mitigation efforts is obvious. Despite comprehensive activities to lower the exposure to arsenic through drinking water in the MINIMat cohort and a decreasing median arsenic concentration in drinking water (Kippler et al., 2016; Vahter et al., 2006b), many of the children still had very high arsenic exposure at 10 years, some even higher than earlier in life. This may indicate that families had new wells constructed without analyzing the water for arsenic, or even that the well-water arsenic problem is being forgotten (Human Rights Watch, 2016). An additional problem is the exposure through food, which contributed to the similar median urinary arsenic concentrations at 5 and 10 years of age.

The strengths of this study include the large sample size and the population-based prospective design with repeated assessment of the wide range of arsenic exposure based on different exposure biomarkers, both prenatally and during childhood. Because arsenic has a short half-life in the body (in the order of hours), the urinary arsenic reflects ongoing exposure. Therefore, we also included more long-term exposure biomarkers, i.e., arsenic in erythrocytes of the mothers and in the two cm of hair closest to the scalp of the children, both of which reflect the exposure during the previous few months (Skroder et al., 2017b). Further strengths of the study include consideration of multiple potential confounders, including SES, HOME, maternal IQ, parental education and school attendance, all of which may influence cognitive abilities of the children. The main limitation of the study is the fact that WISC-IV has not been standardized for Bangladeshi children. As this may give rise to low scoring when scaled to U.S. standards, the cognitive assessment data was expressed as raw scores. Because some of the associations appeared to be non-linear even after log-transformation, we used quintiles of arsenic exposure biomarkers, with the first quintile as reference. Generally, the estimate for Full developmental score in the fifth quintile (with very wide concentrations ranges, e.g. 163–940 μg/L for urinary arsenic at 10 years) was smaller than those in quintiles 3–4, especially in the boys. The reason for this in not known, but we found a similar phenomenon in the evaluation of infant growth in relation to prenatal arsenic exposure (Saha et al., 2012). Part of the explanation for a weaker estimate in the last quintile might be found in an arsenic-related increase in child morbidity (Rahman et al., 2017a), which tends to be overrepresented in boys (Ahmed et al., 2017; Raqib et al., 2009), potentially increasing the loss to follow-up of the most sensitive children. However, we cannot exclude residual confounding. For example, there was a complex inverse relationship between arsenic and manganese in drinking water (Kippler et al., 2016), with water manganese concentrations in arsenic quintile five being less than 10% of those in arsenic quintile one. Another limitation is the lack of continuous lifetime exposure data, why we were not able to evaluate the potential impact of different exposure scenarios across life.

5. Conclusions

Even fairly low early prenatal and concurrent childhood exposure to arsenic from well water and food was associated with impaired cognitive function in school-aged children. However, the time point of the exposure appeared to influence the impact, with the early prenatal exposure showing inverse associations with test results at lower exposure levels, mainly in girls and with more sub-tests, than did the childhood exposure. The effect estimate corresponded to about 0.2 SD of the Full developmental score at the most, which may easily be compensated for in the individual child. Yet, it may be important on a population basis, considering the prevalence of elevated concentrations of arsenic in drinking water and food in Bangladesh and many other places world-wide. Still, other arsenic-related health effects in children may be more critical from a public health perspective. Arsenic exposure causes developmental immunotoxicity, which has been linked to increased child morbidity and mortality (Ahmed et al., 2014; Farzan et al., 2016; Smith et al., 2012), as well as cancer later in life (Roh et al., 2018; Steinmaus et al., 2014). However, a link between immune function and brain development has also been proposed (Cowan and Petri 2018).

CRediT authorship contribution statement

Marie Vahter: Conceptualization, Funding acquisition, Methodology, Project administration, Formal analysis, Writing - original draft. **Helena Skröder:** Data curation, Visualization. **Syed Moshfiqur Rahman:** Supervision. **Michael Levi:** Validation. **Jena Derakhshani Hamadani:** Validation. **Maria Kippler:** Conceptualization, Data curation, Formal analysis, Supervision.

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.

Acknowledgements

We thank all participating families, everybody involved in the collection of samples and information, as well as those that have been involved in sample handling and trace element analyses over the years. The study was funded by the Swedish Research Council (grants 2013-02269, 2015-03206, 2015-03655, 2017-01172), the Swedish Research Council Formas (grant 210-2013-751), the Swedish International

Development Cooperation Agency (Sida) (grants 2002-067, 2003-201A, 2015-03206), Karolinska Institutet, and International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105723.

References

Ahmed, S., Akhtar, E., Roy, A., von Ehrenstein, O.S., Vahter, M., Wagatsuma, Y., Raqib, R., 2017. Arsenic exposure alters lung function and airway inflammation in children: a cohort study in rural Bangladesh. Environ. Int. 101, 108–116.

Ahmed, S., Moore, S.E., Kippler, M., Gardner, R., Hawlader, M.D., Wagatsuma, Y., Raqib, R., Vahter, M., 2014. Arsenic exposure and cell-mediated immunity in pre-school children in rural Bangladesh. Toxicol. Sci. 141, 166–175.

Attreed, S.E., Navas-Acien, A., Heaney, C.D., 2017. Arsenic and immune response to infection during pregnancy and early life. Curr. Environ. Health Rep. 4, 229–243.

Broberg, K., Ahmed, S., Engstrom, K., Hossain, M.B., Jurkovic Mlakar, S., Bottai, M., Grander, M., Raqib, R., Vahter, M., 2014. Arsenic exposure in early pregnancy alters genome-wide DNA methylation in cord blood, particularly in boys. J. Dev. Orig. Health Dis. 5, 288–298.

Caldwell, B.M., Bradley, R.H., 2003. Home inventory and administration manual. University of Arkansas for Medical Sciences and University of Arkansas at Little Rock.

Chattopadhyay, S., Bhaumik, S., Purkayastha, M., Basu, S., Nag Chaudhuri, A., Das Gupta, S., 2002. Apoptosis and necrosis in developing brain cells due to arsenic toxicity and protection with antioxidants. Toxicol Lett 136, 65–76.

Concha, G., Vogler, G., Lezcano, D., Nermell, B., Vahter, M., 1998. Exposure to inorganic arsenic metabolites during early human development. Toxicol. Sci. 44, 185–190.

Cowan, M., Petri Jr., W.A., 2018. Microglia: immune regulators of neurodevelopment. Front. Immunol. 9, 2576.

Desai, G., Barg, G., Queirolo, E.I., Vahter, M., Peregalli, F., Manay, N., Kordas, K., 2018. A cross-sectional study of general cognitive abilities among Uruguayan school children with low-level arsenic exposure, potential effect modification by methylation capacity and dietary folate. Environ. Res. 164, 124–131.

EFSA, E.F.S.A. Dietary exposure to inorganic arsenic in the European population. EFSA Journal 2014;12.

Farzan, S.F., Li, Z., Korrick, S.A., Spiegelman, D., Enelow, R., Nadeau, K., Baker, E., Karagas, M.R., 2016. Infant infections and respiratory symptoms in relation to in utero arsenic exposure in a U.S Cohort. Environ. Health Perspect. 124, 840–847.

Gardner, R., Hamadani, J., Grander, M., Tofail, F., Nermell, B., Palm, B., Kippler, M., Vahter, M., 2011a. Persistent exposure to arsenic via drinking water in rural Bangladesh despite major mitigation efforts. Am. J. Public Health 101 (Suppl 1), S333–S338.

Gardner, R.M., Nermell, B., Kippler, M., Grander, M., Li, L., Ekstrom, E.C., Rahman, A., Lonnerdal, B., Hoque, A.M., Vahter, M., 2011b. Arsenic methylation efficiency increases during the first trimester of pregnancy independent of folate status. Reprod. Toxicol. 31, 210–218.

Gardner, R.M., Kippler, M., Tofail, F., Bottai, M., Hamadani, J., Grander, M., Nermell, B., Palm, B., Rasmussen, K.M., Vahter, M., 2013. Environmental exposure to metals and children's growth to age 5 years: a prospective cohort study. Am. J. Epidemiol. 177, 1356–1367.

Grandjean, P., Landrigan, P.J., 2014. Neurobehavioural effects of developmental toxicity. Lancet Neurol. 13, 330–338.

Gustin, K., Tofail, F., Vahter, M., Kippler, M., 2018. Cadmium exposure and cognitive abilities and behavior at 10years of age: a prospective cohort study. Environ. Int. 113, 259–268.

Hamadani, J.D., Grantham-McGregor, S.M., Tofail, F., Nermell, B., Fangstrom, B., Huda, S.N., Yesmin, S., Rahman, M., Vera-Hernandez, M., Arifeen, S.E., Vahter, M., 2010. Pre- and postnatal arsenic exposure and child development at 18 months of age: a cohort study in rural Bangladesh. Int. J. Epidemiol. 39, 1206–1216.

Hamadani, J.D., Tofail, F., Nermell, B., Gardner, R., Shiraji, S., Bottai, M., Arifeen, S.E., Huda, S.N., Vahter, M., 2011. Critical windows of exposure for arsenic-associated impairment of cognitive function in pre-school girls and boys: a population-based cohort study. Int. J. Epidemiol. 40, 1593–1604.

Hossain, M.B., Ahmed, A.S.S., Sarker, M.S.I., 2018. Human health risks of Hg, As, Mn, and Cr through consumption of fish, Ticto barb (Puntius ticto) from a tropical river, Bangladesh. Environ. Sci. Pollut. Res. Int. 25, 31727–31736.

Human Rights Watch, 2016. Nepotism and Neglect The Failing Response to Arsenic in the Drinking Water of Bangladesh's Rural Poor. Human Rights Watch report, April 6, 2016. 112 pp. https://www.hrw.org/report/2016/04/06/nepotism-and-neglect/failing-response-arsenic-drinking-water-bangladeshs-rural (downloaded 2019).

IARC. Arsenic, metals, fibres, and dust. IARC Monographs, available at http://monographsiarcfr/ENG/Monographs/vol100C/mono100C-8pdf 2012;Volume 100 C.

Khan, K., Wasserman, G.A., Liu, X., Ahmed, E., Parvez, F., Slavkovich, V., Levy, D., Mey, J., van Geen, A., Graziano, J.H., Factor-Litvak, P., 2012. Manganese exposure from drinking water and children's academic achievement. Neurotoxicology 33, 91–97.

Kippler, M., Skroder, H., Rahman, S.M., Tofail, F., Vahter, M., 2016. Elevated childhood exposure to arsenic despite reduced drinking water concentrations – a longitudinal cohort study in rural Bangladesh. Environ. Int. 86, 119–125.

Kordas, K., Ardoino, G., Coffman, D.L., Queirolo, E.I., Ciccariello, D., Manay, N., Ettinger, A.S., 2015. Patterns of exposure to multiple metals and associations with neurodevelopment of preschool children from Montevideo, Uruguay. J. Environ. Public Health 2015, 493471.

Lindgren, A., Danielsson, B.R., Dencker, L., Vahter, M., 1984. Embryotoxicity of arsenite and arsenate: distribution in pregnant mice and monkeys and effects on embryonic cells in vitro. Acta Pharmacol. Toxicol. (Copenh) 54, 311–320.

Lu, Y., Kippler, M., Harari, F., Grander, M., Palm, B., Nordqvist, H., Vahter, M., 2015. Alkali dilution of blood samples for high throughput ICP-MS analysis-comparison with acid digestion. Clin. Biochem. 48, 140–147.

Nermell, B., Lindberg, A.L., Rahman, M., Berglund, M., Persson, L.A., El Arifeen, S., Vahter, M., 2008. Urinary arsenic concentration adjustment factors and malnutrition. Environ. Res. 106, 212–218.

Pandey, R., Rai, V., Mishra, J., Mandrah, K., Kumar Roy, S., Bandyopadhyay, S., 2017. From the cover: arsenic induces hippocampal neuronal apoptosis and cognitive impairments via an up-regulated BMP2/Smad-dependent reduced BDNF/TrkB signaling in rats. Toxicol. Sci. 159, 137–158.

Persson, L.A., Arifeen, S., Ekstrom, E.C., Rasmussen, K.M., Frongillo, E.A., Yunus, M., 2012. Effects of prenatal micronutrient and early food supplementation on maternal hemoglobin, birth weight, and infant mortality among children in Bangladesh: the MINIMat randomized trial. JAMA 307, 2050–2059.

Rahman, M., Vahter, M., Wahed, M.A., Sohel, N., Yunus, M., Streatfield, P.K., El Arifeen, S., Bhuiya, A., Zaman, K., Chowdhury, A.M., Ekstrom, E.C., Persson, L.A., 2006. Prevalence of arsenic exposure and skin lesions. A population based survey in Matlab, Bangladesh. J. Epidemiol. Community Health 60, 242–248.

Rahman, A., Granberg, C., Persson, L.A., 2017a. Early life arsenic exposure, infant and child growth, and morbidity: a systematic review. Arch. Toxicol. 91, 3459–3467.

Rahman, S.M., Kippler, M., Tofail, F., Bolte, S., Hamadani, J.D., Vahter, M., 2017b. Manganese in drinking water and cognitive abilities and behavior at 10 years of age: a prospective cohort study. Environ. Health Perspect. 125, 057003.

Raqib, R., Ahmed, S., Ahsan, K.B., Kippler, M., Akhtar, E., Roy, A.K., Lu, Y., Arifeen, S.E., Wagatsuma, Y., Vahter, M., 2017. Humoral immunity in arsenic-exposed children in rural bangladesh: total immunoglobulins and vaccine-specific antibodies. Environ Health Perspect 125, 067006.

Raqib, R., Ahmed, S., Sultana, R., Wagatsuma, Y., Mondal, D., Hoque, A.M., Nermell, B., Yunus, M., Roy, S., Persson, L.A., Arifeen, S.E., Moore, S., Vahter, M., 2009. Effects of in utero arsenic exposure on child immunity and morbidity in rural Bangladesh. Toxicol Lett 185, 197–202.

Rocha-Amador, D., Navarro, M.E., Carrizales, L., Morales, R., Calderon, J., 2007. Decreased intelligence in children and exposure to fluoride and arsenic in drinking water. Cad Saude Publica 23 (Suppl 4), S579–S587.

Rodrigues, E.G., Bellinger, D.C., Valeri, L., Hasan, M.O., Quamruzzaman, Q., Golam, M., Kile, M.L., Christiani, D.C., Wright, R.O., Mazumdar, M., 2016. Neurodevelopmental outcomes among 2- to 3-year-old children in Bangladesh with elevated blood lead and exposure to arsenic and manganese in drinking water. Environ. Health 15, 44.

Roh, T., Steinmaus, C., Marshall, G., Ferreccio, C., Liaw, J., Smith, A.H., 2018. Age at exposure to arsenic in water and mortality 30–40 years after exposure Cessation. Am. J. Epidemiol. 187, 2297–2305.

Rosado, J.L., Ronquillo, D., Kordas, K., Rojas, O., Alatorre, J., Lopez, P., Garcia-Vargas, G., Del Carmen Caamano, M., Cebrian, M.E., Stoltzfus, R.J., 2007. Arsenic exposure and cognitive performance in Mexican schoolchildren. Environ. Health Perspect. 115, 1371–1375.

Saha, K.K., Engstrom, A., Hamadani, J.D., Tofail, F., Rasmussen, K.M., Vahter, M., 2012. Pre- and Postnatal Arsenic Exposure and Body Size to Two Years of Age: a Cohort Study in Rural Bangladesh. Environ Health Perspect.

Signes-Pastor, A.J., Vioque, J., Navarrete-Munoz, E.M., Carey, M., Garcia-Villarino, M., Fernandez-Somoano, A., Tardon, A., Santa-Marina, L., Irizar, A., Casas, M., Guxens, M., Llop, S., Soler-Blasco, R., Garcia-de-la-Hera, M., Karagas, M.R., Meharg, A.A., 2019. Inorganic arsenic exposure and neuropsychological development of children of 4–5 years of age living in Spain. Environ. Res. 174, 135–142.

Skroder, H., Kippler, M., Tofail, F., Vahter, M., 2017a. Early-life selenium status and cognitive function at 5 and 10 years of age in Bangladeshi Children. Environ. Health Perspect. 125, 117003.

Skroder, H., Kippler, M., Nermell, B., Tofail, F., Levi, M., Rahman, S.M., Raqib, R., Vahter, M., 2017b. Major limitations in using element concentrations in hair as biomarkers of exposure to toxic and essential trace elements in children. Environ. Health Perspect. 125, 067021.

Smith, A.H., Marshall, G., Liaw, J., Yuan, Y., Ferreccio, C., Steinmaus, C., 2012. Mortality in young adults following in utero and childhood exposure to arsenic in drinking water. Environ. Health Perspect. 120, 1527–1531.

Steinmaus, C., Ferreccio, C., Acevedo, J., Yuan, Y., Liaw, J., Duran, V., Cuevas, S., Garcia, J., Meza, R., Valdes, R., Valdes, G., Benitez, H., VanderLinde, V., Villagra, V., Cantor, K.P., Moore, L.E., Perez, S.G., Steinmaus, S., Smith, A.H., 2014. Increased lung and bladder cancer incidence in adults after in utero and early-life arsenic exposure. Can. Epidemiol. Biomarkers Prev. 23, 1529–1538.

Tofail, F., Vahter, M., Hamadani, J.D., Nermell, B., Huda, S.N., Yunus, M., Rahman, M., Grantham-McGregor, S.M., 2009. Effect of arsenic exposure during pregnancy on infant development at 7 months in rural Matlab, Bangladesh. Environ. Health Perspect. 117, 288–293.

Vahter, M., 2002. Mechanisms of arsenic biotransformation. Toxicology 181–182, 211–217.

Vahter, M., Li, L., Nermell, B., Rahman, A., Arifeen, S.E., Rahman, M., Persson, L.A., Ekström, E.C., 2006a. Arsenic exposure in pregnancy – a population based study in Matlab, Bangladesh. J. Health Popul. Nutr. 24 (2), 236–245.

Vahter, M.E., Li, L., Nermell, B., Rahman, A., El Arifeen, S., Rahman, M., Persson, L.A., Ekstrom, E.C., 2006b. Arsenic exposure in pregnancy: a population-based study in Matlab, Bangladesh. J. Health Popul. Nutr. 24, 236–245.

Wang, S.X., Wang, Z.H., Cheng, X.T., Li, J., Sang, Z.P., Zhang, X.D., Han, L.L., Qiao, X.Y., Wu, Z.M., Wang, Z.Q., 2007. Arsenic and fluoride exposure in drinking water: children's IQ and growth in Shanyin county, Shanxi province China. Environ. Health Perspect. 115, 643–647.

Wang, Y., Wu, H., Fontanet, P., Codeluppi, S., Akkuratova, N., Petitpre, C., Xue-Franzen, Y., Niederreither, K., Sharma, A., Da Silva, F., Comai, G., Agirman, G., Palumberi, D., Linnarsson, S., Adameyko, I., Moqrich, A., Schedl, A., La Manno, G., Hadjab, S., Lallemend, F., 2019. A cell fitness selection model for neuronal survival during development. Nat. Commun. 10, 4137.

Wasserman, G.A., Liu, X., Loiacono, N.J., Kline, J., Factor-Litvak, P., van Geen, A., Mey, J.L., Levy, D., Abramson, R., Schwartz, A., Graziano, J.H., 2014. A cross-sectional study of well water arsenic and child IQ in Maine schoolchildren. Environ. Health 13, 23.

Wasserman, G.A., Liu, X., Parvez, F., Ahsan, H., Factor-Litvak, P., Kline, J., van Geen, A., Slavkovich, V., Loiacono, N.J., Levy, D., Cheng, Z., Graziano, J.H., 2007. Water arsenic exposure and intellectual function in 6-year-old children in Araihazar, Bangladesh. Environ. Health Perspect. 115, 285–289.

Wasserman, G.A., Liu, X., Parvez, F., Factor-Litvak, P., Ahsan, H., Levy, D., Kline, J., van Geen, A., Mey, J., Slavkovich, V., Siddique, A.B., Islam, T., Graziano, J.H., 2011. Arsenic and manganese exposure and children's intellectual function. Neurotoxicology 32, 450–457.

WHO. WHO child growth standards: Lenght/height-for-age, weight-for-age, weight-for-lenght, weight-for-height, and body mass index-for-age: Methods and development. in: Group W.M.G.R.S., ed. Geneva; 2006.

Winterbottom, E.F., Moroishi, Y., Halchenko, Y., Armstrong, D.A., Beach, P.J., Nguyen, Q.P., Capobianco, A.J., Ayad, N.G., Marsit, C.J., Li, Z., Karagas, M.R., Robbins, D.J., 2019. Prenatal arsenic exposure alters the placental expression of multiple epigenetic regulators in a sex-dependent manner. Environ. Health 18, 18.

von Ehrenstein, O.S., Poddar, S., Yuan, Y., Mazumder, D.G., Eskenazi, B., Basu, A., Hira-Smith, M., Ghosh, N., Lahiri, S., Haque, R., Ghosh, A., Kalman, D., Das, S., Smith, A.H., 2007. Children's intellectual function in relation to arsenic exposure. Epidemiology 18, 44–51.