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Associations of gestational and childhood exposure to lead, cadmium, and fluoride with cognitive abilities, behavior, and social communication at 4 years of age: NICE birth cohort study

Mariza Kampouri [a], Eric Zander [b], Klara Gustin [a], Anna Sandin [c], Malin Barman [a,d], Ann-Sofie Sandberg [d], Agnes E. Wold [e], Sven Bölte [b,f,g], Maria Kippler [a,*], Marie Vahter [a]

[a] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[b] Center of Neurodevelopmental Disorders (KIND), Department of Women's and Children's Health, Centre for Psychiatry Research, Karolinska Institutet & Region Stockholm, Stockholm, Sweden
[c] Department of Clinical Science, Pediatrics, Sunderby Research Unit, Umeå University, Sweden
[d] Food and Nutrition Science, Department of Life Sciences, Chalmers University of Technology, Gothenburg, Sweden
[e] Institute of Biomedicine, Department of Infectious Diseases, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[f] Child and Adolescent Psychiatry, Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden
[g] Curtin Autism Research Group, Curtin School of Allied Health, Curtin University, Perth, Australia

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ABSTRACT

Background: Early-life lead exposure affects cognitive development and emerging evidence suggests similar effects of cadmium and fluoride.
Objective: To assess the impact of gestational and childhood exposure to lead, cadmium, and fluoride on cognitive abilities and behavioral and social communication problems.
Methods: We studied 470 pregnant women (gestational week 29) and their 4-year-old children from the NICE cohort in northern Sweden. Concentrations of erythrocyte lead and cadmium and urinary cadmium were measured using inductively coupled plasma mass spectrometry and urinary fluoride with an ion-selective electrode. Urinary concentrations were specific-gravity adjusted. Associations of $\log_2$-transformed exposure concentrations with cognitive abilities (full-scale IQ and verbal comprehension by *Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition)*, behavioral problems (*Child Behavior Checklist),* and social communication (*Social Responsiveness Scale-Second Edition*) were evaluated with multivariable-adjusted linear regression analysis.
Results: Both gestational and cord erythrocyte lead concentrations were non-significantly inversely associated with child cognitive abilities (full-scale IQ: *B* [95%CI]: −1.2 [-2.9, 0.5] and −1.6 [-3.7, 0.4], respectively; per doubling of exposure). Similarly, both gestational and child urinary cadmium were inversely associated with cognitive abilities (full-scale IQ: −1.1 [-2.5, 0.3] and −1.1 [-2.5, 0.4], verbal comprehension: −1.2 [-3.1, 0.6] and −1.4 [-3.4, 0.6], respectively). Urinary fluoride concentrations showed no association with cognitive abilities. However, gestational fluoride was associated with increasing externalizing problems (0.9 [-0.3, 2.0]) and ADHD raw scores (0.3 [0.0, 0.6]). Childhood erythrocyte lead and urinary cadmium were non-significantly associated with increased behavioral problems (lead with total problems: 1.2 [-0.4, 2.9] and internalizing problems: 1.5 [-0.4, 3.4]; cadmium with externalizing problems: 1.1 [-0.2, 2.4]).
Conclusion: Despite non-significant associations, both lead and cadmium exposure showed consistent inverse associations with cognitive abilities at 4 years, whereas associations with behavioral problems were less conclusive, especially for cadmium. Results on fluoride indicated association with externalizing problems, including ADHD, but prevalence of behavioral problems was low, increasing uncertainty.

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

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1. Introduction

Development of the central nervous system relies on an interplay between genes and the environment, progressing through distinct processes (*i.e.*, proliferation, differentiation, migration, synapse formation, myelination), starting from the early prenatal period and extending throughout childhood and adolescence (Rice and Barone, 2000). The developing brain is highly susceptible to environmental stressors, including toxic chemicals (Grandjean and Landrigan, 2006).

Lead is a well-established neurotoxicant that is often present in drinking water, food, soil, dust, and various consumer products (EFSA, 2010; Grandjean and Herz, 2015). Early-life lead exposure affects neurodevelopment even at very low levels, displaying no apparent threshold (Bellinger et al., 2016; Canfield et al., 2003; EFSA, 2010; Lanphear et al., 2005). Cadmium exposure, primarily derived from food and tobacco smoking, has also been associated with decreased child cognitive abilities in prospective studies (Flannery et al., 2022; Sanders et al., 2015), but evidence remains limited. Fluoride is a non-metallic element which is naturally present in drinking water in certain regions and commonly added to dental care products, drinking water, table salt, or milk to prevent dental decay (EFSA, 2013). Cross-sectional studies conducted in regions with elevated fluoride concentrations in drinking water, as well as experimental studies, have reported a link to lower cognition (Grandjean, 2019). Moreover, recent prospective studies have suggested that especially prenatal fluoride exposure is linked to lower cognitive abilities even at exposure levels that are currently considered beneficial for caries prevention (Grandjean et al., 2022).

In addition to cognitive effects, low-level lead exposure has been linked to behavioral problems in children and adolescents (Bauer et al., 2020). Behavioral effects of cadmium exposure remain understudied with inconclusive findings (Flannery et al., 2022; Rodríguez-Barranco et al., 2013), which also applies to fluoride exposure (Fiore et al., 2023).

In the present study, we aimed to determine the potential impact of gestational and early-life low-level exposure to lead, cadmium, and fluoride on child cognition, as well as behavioral and social communication problems at 4 years of age in a Swedish birth cohort. In Sweden, fluoride is not added to drinking water, but concentrations have been shown to vary naturally (Aggeborn and Öhman, 2021; Aneblom et al., 2005).

2. Methods

2.1. Study population

NICE (Nutritional Impact on the Immunological Maturation during Childhood in relation to the Environment) is a prospective birth-cohort in the Norrbotten county, northern Sweden, established by recruitment of pregnant women between 2015 and 2018 (NCT05809479) (Barman et al., 2018). The main objectives are to assess the impact of early-life environment on immune maturation, allergy development, growth, cognitive and behavioral development, and oral health. During the first visit to the local maternity units, expecting parents were given information about the NICE study. If interested in participation, they received more comprehensive information about the study at the routine ultrasound scan around gestational week 18, along with a written consent form to sign. The inclusion criteria for participation were residency in the Norrbotten region, planned delivery at Sunderby Hospital, and the ability to communicate in the Swedish language.

Initially, 655 pregnancies were enrolled in the NICE study (Supplemental Fig. 1). After excluding families already participating with a previous child, twin pregnancies, miscarriages, stillbirths, and one participant who withdrew consent, 629 mother-infant pairs remained eligible for the present study, out of which 475 children attended the 4-year follow-up, including the assessment of cognitive abilities. Loss to follow-up was impacted by the COVID-19 pandemic, which coincided with a large part of the testing period and caused major difficulties in traveling and visiting the hospital. In total, 472 children completed the assessment of cognitive abilities, while the questionnaires for behavioral problems and social communication problems were completed by caregivers for 382 and 417 children, respectively. After consideration of the exposure and covariate data availability, 470 children have been included in at least one of the presented models. Models of cognitive abilities with maternal erythrocyte metal concentrations and maternal urinary cadmium and fluoride included 439, 437, and 434 children, respectively, corresponding models with child exposure biomarkers included 255, 400, and 399 children, respectively. We had fewer blood samples from the children as we did not pursue the children who hesitated to give blood. Models with metal biomarkers in cord blood included 303 children, the loss was mainly due to lack of enough personnel at the delivery ward. Details for the behavior and social communication problems' models are provided in Supplemental Fig. 1.

This study was conducted in accordance with the ethical standards of the Helsinki declaration, and it was approved by the Regional Ethical Review Board in Umeå, Sweden. Written and verbal information had been given to the participating parents before they gave their written consent.

2.2. Exposure assessment

Exposure to lead and cadmium was assessed by concentrations in maternal and child erythrocytes, reflecting recent exposure. Cadmium exposure was also assessed by concentrations in urine, reflecting long-term exposure due to accumulation in the kidneys (Järup and Åkesson, 2009). Erythrocyte concentrations of lead and cadmium have an advantage over whole blood concentrations by being less affected by the pregnancy-related plasma expansion, as almost all of lead and cadmium in blood is localized in the erythrocytes (Carlson and Friberg, 1957; EFSA, 2010; Schultze et al., 2014). We also measured the concentrations of lead and cadmium in cord blood erythrocytes. As cadmium accumulates in the placenta leaving low direct exposure of the fetus (Kippler et al., 2010), maternal erythrocyte cadmium does not reflect fetal exposure. Lead, on the other hand, easily passes through the placenta to the fetus (EFSA, 2010). Maternal blood and spot urine samples were collected at the local maternity clinics, at approximately gestational week 29 (SD: 1.4, range: 25–36) (Barman et al., 2018; Gustin et al., 2020, 2021). Cord blood samples were collected at delivery and blood and spot urine samples from the children were collected in connection with the 4-year follow-up, all at Sunderby hospital. Blood samples were collected in 6 mL trace element-free Na-heparin tubes (Greiner bio-one, Kremsmünster, Austria). Spot urine samples were collected in urine collection cups and then transferred to trace element-free 24-mL polyethylene bottles. Samples collected at the local maternity clinics were stored at 4 °C until transported cold to the hospital laboratory on the same or the following workday. At the hospital laboratory, blood samples were centrifuged for 5 min at 2400 rpm (Hettich Rotina 420, Hettich Lab Technology, Tuttlingen, Germany). The erythrocyte fraction was retained in the collection tube and stored together with urine at −20 °C for a very short period and then at −80 °C until transported frozen to Karolinska Institutet, Stockholm, Sweden, for trace element analyses.

Metal concentrations were measured with inductively coupled plasma mass spectrometry (ICP-MS; Agilent 7900, Agilent Technologies, Tokyo, Japan), equipped with an octopole reaction system (Gustin et al., 2020). The limit of detection (LOD) for maternal erythrocyte lead and cadmium was 0.11 μg/kg and 0.04 μg/kg, respectively, and for maternal urinary cadmium it was 0.003 μg/L (Gustin et al., 2020). The LOD for erythrocyte lead and cadmium in cord blood was 0.0045 μg/kg and 0.0032 μg/kg, respectively. The LOD for child erythrocyte lead and cadmium was 0.052 μg/kg and 0.017 μg/kg, respectively, and for urinary cadmium it was 0.001 μg/L. Lead concentrations were above the LOD in all samples. Cadmium concentrations were below the respective LOD in 73 cord blood erythrocyte samples and in 7 child erythrocyte

samples, and they were all replaced by LOD/$\sqrt{2}$, since some values were negative.

Fluoride concentrations in urine were measured using an ion selective electrode (Orion 9609BNWP and Orion Star A214 pH/ISE meter; Thermo Fisher Scientific, Waltham, MA USA) (Kampouri et al., 2022). The estimated LOD for maternal urinary fluoride was 0.05 mg/L (Kampouri et al., 2022) and for child urine it was 0.02 mg/L. Two maternal urine samples had fluoride concentrations below the LOD, but their concentrations were kept as measured, since they both had positive values. The quality control of the analyses of the maternal exposure biomarkers has been previously presented in detail (Gustin et al., 2020; Kampouri et al., 2022) and the quality control of child exposure and cord blood biomarkers is presented in Supplemental Table 1.

Urine concentrations were adjusted for specific gravity to control for the variation in urine dilution (Nermell et al., 2008). Specific gravity was measured with a digital refractometer (EUROMEX RD712, Clinical Refractometer, Holland), and all urinary concentrations were adjusted to the median specific gravity (maternal urine: median = 1.017, child urine: median = 1.016) applying the following formula: adjusted urinary concentration = unadjusted urinary concentration × (specific gravity$_{median}$-1)/(specific gravity$_{sample}$-1).

2.3. Outcome assessment

Cognitive assessment at 4 years of age (mean [SD] = 4.2 [0.1] years) was conducted using the Swedish version of the *Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV;* Pearson Sweden AB; https://www.pearsonclinical.se/wppsi-iv) (Wechsler, 2012). The *WPPSI-IV* is a normed individually administered psychometric test designed to assess intelligence in children aged 2.5–7.6 years (Wechsler, 2012). The *WPPSI-IV* assesses Full-Scale IQ representing overall intellectual functioning across five domains (verbal comprehension, visual-spatial, fluid reasoning, working memory, and processing speed) (mean [SD]: 100 [15] age-standardized scores). In the NICE study, full scale IQ was assessed (sum of scores in information, similarities, block design, matrix reasoning, picture memory and bug search), along with verbal comprehension (sum of scores in information and similarities). Cognitive assessment with the *WPPSI-IV* was conducted by research assistants (nurses specialized in pediatrics), trained and supervised by a licensed psychologist (second author).

Behavioral problems were assessed with the *Child Behavior Checklist (CBCL)* (Achenbach and Edelbrock, 1991). The *CBCL* is a normed caregiver-rating questionnaire (web-based) designed to screen for child behavioral problems (Achenbach and Edelbrock, 1991). For children aged 1.5–5 years, the caregiver completes 100 items on child behavior addressing the past two months on a 3-point Likert scale (not true, somewhat or sometimes true, very true or often true). The items are summarized into two broad-band syndrome scales, namely Externalizing and Internalizing problems, along with a Total problems scale (sum of internalizing, externalizing, and other problems) (mean [SD]: 50 [10] T-scores). The CBCL also includes scales assessing behavioral problems in specific domains, including an Attention-Deficit/Hyperactivity Disorder (ADHD) scale designed to evaluate problems related to attention difficulties and hyperactivity. Increasing scores in the *CBCL* indicate more severe child behavior problems. Social communication problems were assessed using the *Social Responsiveness Scale, Second Edition (SRS-2)* (Bruni, 2014). The *SRS-2* is a normed caregiver-rating scale designed to quantitatively assess social communication to quantify autistic behaviors (Bruni, 2014). For children aged 4.0 years to 17.11, the caregiver responds to 65 items on a 4-point Likert scale (not true, sometimes true, often true, almost always true). Item scores are summed-up to a total score (mean [SD]: 50 [10] T-scores) with increasing scores indicating higher social communication atypicality.

2.4. Covariates

Information on maternal age (years), early-pregnancy body mass index [BMI (kg/m^2)], parity (number of births), education (elementary school, high school, or university), smoking prior to pregnancy (never, sometimes, or daily), gestational age at delivery (gestational week), the child's birth weight (kg), sex (male, female), and date of birth was obtained from the hospital records. We used data on smoking prior to pregnancy (never/ever) instead of during pregnancy, since only four women smoked during pregnancy, and pre-pregnancy smoking might still have influenced both the exposures and the outcomes. We did not adjust for alcohol intake, as no woman reported alcohol consumption during pregnancy.

2.5. Statistical analyses

Statistical analyses were performed using the software Stata/IC 13.0 (StataCorp, TX, USA). *P-values* below 0.05 were considered statistically significant, but we also considered overall consistency and robustness of the results (Greenland et al., 2016), as well as biological plausibility. Bivariate correlations between the exposure biomarkers (erythrocyte concentrations of cadmium and lead, and urinary concentrations of cadmium and fluoride), the outcomes (*WPPSI-IV:* full-scale IQ score, *WPPSI-IV:* verbal comprehension score, *CBCL*: total problems score, *CBCL*: externalizing problems score, *CBCL*: internalizing problems score; *CBCL:* ADHD raw score, *SRS-2*: total score) and all potential covariates were initially explored using Spearman rank test, Mann-Whitney *U* test, or Kruskal-Wallis test (combined with Dunn's test for post-hoc pairwise comparisons), depending on the type of data.

A directed acyclic graph (DAG) was drawn, using DAGitty version 3.0 (https://www.dagitty.net), to facilitate the selection of the adjustment factors (Supplemental Fig. 2). Based on the DAG structure, the minimal sufficient adjustment set included maternal education (categorical; no university degree or university degree), maternal smoking before pregnancy (categorical; no or yes), and parity (categorical; primiparous or multiparous). Child age at assessment (continuous; years) and sex (categorical; boy or girl) were a priori selected factors that were included in the adjustment set. The metal and fluoride concentrations were log$_2$-transformed (due to right-skewedness). Generalized additive models, adjusted for the full set of potential confounders, were utilized to identify the most fitting model based on visual assessment combined with a *P*-gain threshold of 0.1 (Supplemental Figs. 3–11). No evidence of deviation from linearity was observed in any of the models.

Linear regression analyses were performed to calculate the associations [regression coefficients (*Bs*) and their corresponding 95% confidence intervals (CIs)] between every doubling in the exposure (one log$_2$ unit increase; gestational, cord blood, and childhood lead concentrations in erythrocytes, gestational and childhood cadmium concentrations in erythrocytes, as well as gestational and childhood cadmium and fluoride concentrations in urine) and the outcomes (*WPPSI-IV:* full-scale IQ score, *WPPSI-IV:* verbal comprehension score, *CBCL*: total problems score, *CBCL*: externalizing problems score, *CBCL*: internalizing problems score; *CBCL:* ADHD raw score, *SRS-2*: total score). Cadmium cord blood concentrations were categorized into two groups, below and above the LOD, and inserted as such in the regression models, since 23% of the samples had concentrations below the LOD. Given the association of early-life fluoride and cadmium exposure with increased ADHD symptoms in previous studies (Bashash et al., 2018; Flannery et al., 2022), we conducted additional analyses using the raw scores in attention-deficit-hyperactivity-disorder scale of *CBCL*. Model 1 presents crude associations and Model 2 associations were adjusted for maternal age, maternal education, maternal smoking, parity, and child age and sex. Potential modification of the associations by child sex was assessed by adding a multiplicative interaction term in the adjusted models and stratifying the models by child sex when appropriate (*P*-for-interaction <0.05).

Sensitivity analyses were conducted for gestational and childhood lead and cadmium exposure models, repeating the analyses only for children whose mothers were non-smokers prior to pregnancy. Additionally, childhood lead, cadmium, and fluoride exposure models were repeated with further adjustments for the corresponding gestational concentrations or corresponding cord blood concentrations. Fluoride exposure models were repeated using urinary concentrations in their original scale (per 0.5 mg/L), and also when limited to urinary concentrations below the 98th percentile. We also repeated the models of maternal fluoride concentrations with additional adjustment for the season of urine sampling (autumn, winter, spring, or summer).

3. Results

3.1. Background characteristics

The background characteristics of the mother-child pairs are presented in Table 1. The mean maternal age at child delivery was 31 years (SD = 5), 47% were primiparous, 72% had a university degree (n = 337), and 6% smoked before pregnancy (n = 27). Participating children were 4.2 years old (range: 3.9–4.7) at the time of the assessment, and 53% of them were girls (n = 251). The mean standardized score in *WPPSI-IV*-full scale IQ of the tested children was 110 (SD = 12, range: 62–151). The parents who completed the *CBCL* rated their children's behavioral problems, on average, low (total-problems mean [SD, range]: 41 [9, 28–82]) T-scores). The distribution of *WPPSI-IV*, *CBCL*, and *SRS-2* scores by maternal and child characteristics are shown in Supplemental Table 2. The correlation between *WPPSI-IV* full-scale IQ scores and *CBCL* scores (n = 349) was −0.12 (P=0.032) for total problems, −0.17 (P = 0.001) for externalizing problems, and −0.09 (P=0.091) for internalizing problems.

The distribution characteristics of maternal and child lead, cadmium, and fluoride concentrations, as well as of the lead and cadmium cord blood concentrations for all children are presented in Table 2. All cord blood and child concentrations are also presented for boys and girls separately (Table 2). There were no differences in child metal and fluoride concentrations by child sex. The bivariate associations among cadmium, lead, and fluoride concentrations and with maternal background characteristics are presented in Supplemental Table 3. Gestational erythrocyte lead concentrations were positively correlated with cord blood lead (*rho* = 0.69, $P < 0.001$) and lead concentrations at 4 years (*rho* = 0.43, $P < 0.001$). Erythrocyte lead concentrations in cord blood were also positively correlated with lead concentrations at 4 years (*rho* = 0.42, $P < 0.001$). Gestational urinary cadmium concentrations were positively correlated with erythrocyte cadmium concentrations in gestation (*rho* = 0.40; $P < 0.001$), and child urinary cadmium concentrations were positively correlated with child erythrocyte cadmium concentrations (*rho* = 0.26, $P < 0.001$) as well as with child urinary fluoride concentrations (*rho* = 0.25, $P < 0.001$). Gestational urinary cadmium concentrations were positively correlated with maternal age (*rho* = 0.29, $P < 0.001$), and slightly higher in women who smoked prior to pregnancy (n = 27; median: 0.12 μg/L compared to 0.10 μg/L, P=0.020). Smokers had also markedly higher erythrocyte cadmium concentrations compared to non-smokers (median 0.50 μg/kg compared to 0.28 μg/kg, $P < 0.001$). Urinary fluoride concentrations were slightly higher in women with a university degree compared to those who had not completed university (median: 0.74 mg/L vs 0.68 mg/L, P=0.003).

Table 1
Characteristics of the mother-child pairs included in the study and comparison with non-participants.

	Participants[a] (n = 470)		Non-participants[a] (n = 159)		*P*-value[b]
	N	Mean (SD) or %	N	Mean (SD) or %	
Maternal age (years)	470	30.7 (4.6)	158	30.2 (5.1)	0.267
BMI in early pregnancy (kg/m^2)	459	25.4 (4.9)	155	25.4 (4.8)	0.545
Parity (%)	470				
Primiparous	221	47	83	55	0.090
Multiparous	249	53	68	45	
Maternal education (university; %)	470				
Yes	337	72	90	60	0.004
No	133	28	60	40	
Maternal pre-pregnancy smoking (%)	470				
No	443	94	134	91	0.114
Yes	27	6	14	9	
Child sex (%)	470				
Girls	251	53	82	53	0.973
Boys	219	47	72	47	
Preterm birth (<37 gestational week)	470		151		0.060
No	453	96	140	93	
Yes	17	4	11	7	
Birthweight	469	3611 (548)	150	3517 (579)	0.221
Child age at assessment (years)	452	4.2 (0.1)			
WPPSI-IV: Full-scale score	452	110 (12)			
WPPSI-IV: Verbal comprehension score	452	108 (17)			
CBCL: Total problems score	364	41 (9)			
CBCL: Externalizing problems score	364	41 (9)			
CBCL: Internalizing problems score	364	42 (10)			
CBCL: ADHD raw score	364	2.2 (2.1)			
SRS-2: Total problems score	400	48 (6)			

Abbreviations: SD: standard deviation; BMI: body mass index; WPPSI-IV: *Wechsler Preschool and Primary Scale of Intelligence - Fourth Edition*; *CBCL: Child Behaviour Checklist*; *SRS-2: Social Responsiveness Scale - Second Edition.*

[a] Both participants and non-participants include live singleton children recruited in the NICE study; participants are included in at least one of the models, provided they have data on at least one of the studied exposures (erythrocyte lead, urinary cadmium, erythrocyte cadmium, and urinary fluoride at gestation, erythrocyte cadmium and lead in cord blood or erythrocyte lead, urinary cadmium, erythrocyte cadmium, and urinary fluoride at 4 years), one of the outcomes (*Wechsler Preschool and Primary Scale of Intelligence IV* [*WPPSI-IV*], *Child Behaviour Checklist [CBCL*], and *Social Responsiveness Scale-2 [SRS-2*]), and complete data on the adjustment factors (maternal age, maternal education, parity, maternal smoking before pregnancy, child sex, and child age at assessment).

[b] *P*-values are obtained using Mann-Whitney and chi^2 tests, depending on the type of the data.

Table 2
Lead, cadmium, and fluoride concentrations in mothers during pregnancy (≈gestational week 29) and children at 4 years of age; for all children, and for girls and boys separately.

	All participants		5th-95th perc.	Range	Girls		Boys		*P*-value [a]
	N	Median			N	Median	N	Median	
Gestational erythrocyte lead (μg/kg)	456	11.2	5.9–25.3	3.8–147.8	–	–	–	–	–
Cord blood erythrocyte lead (μg/kg)	314	7.8	4.0–18.8	2.5–37.0	172	7.8	142	8.0	0.653
Child erythrocyte lead (μg/kg)	250	16.0	7.8–41.4	5.4–85.7	139	15.6	111	16.4	0.882
Gestational urinary cadmium (μg/L)[b]	454	0.10	0.04–0.27	0.02–0.97	–	–	–	–	–
Gestational erythrocyte cadmium (μg/kg)	456	0.29	0.14–0.68	0.05–5.69	–	–	–	–	–
Cord blood erythrocyte cadmium (μg/kg)	314	0.04	0.002–0.131	0.002–1.094	172	0.04	142	0.04	0.636
Child urinary cadmium (μg/L)[b]	398	0.04	0.02–0.10	0.003–0.36	203	0.04	195	0.04	0.128
Child erythrocyte cadmium (μg/kg)	250	0.15	0.06–0.26	0.01–0.34	139	0.15	111	0.16	0.509
Gestational urinary fluoride (mg/L)[b]	441	0.72	0.3–1.88	0.07–6.4	–	–	–	–	–
Child urinary fluoride (mg/L)[b]	397	0.86	0.31–2.26	0.04–5.7	203	0.81	194	0.90	0.525

Abbreviations: IQR: interquartile range; perc: percentile.
[a] *P*-values for differences between girls and boys were obtained using the Mann-Whitney test.
[b] Urinary cadmium and fluoride concentrations are adjusted to the median specific gravity (1.017 for the mothers and 1.016 for the children).

3.2. Associations of metal and fluoride exposure with cognitive abilities

In the adjusted linear regression analyses, gestational erythrocyte lead concentrations appeared associated with lower cognitive abilities (full-scale: *B* [95%CI]: −1.2 [−2.9, 0.5], per doubling of exposure; Model 2, Table 3). The estimate for verbal comprehension was the same but the CI was wider. These adjusted estimates were only marginally decreased compared to the unadjusted models (Table 3) and did not substantially change when the models were repeated only in children whose mothers were non-smokers (Supplemental Table 4). Erythrocyte lead concentrations in cord blood also tended to be inversely associated with full-scale IQ (B [95% CI]: −1.6 [−3.7, 0.4]), and the estimates were slightly higher compared to those in the models of maternal gestational exposure (Table 3). Child erythrocyte lead concentrations showed no cross-sectional association with cognitive abilities (Table 3). We did not observe any evidence of interaction by child sex in the associations (Table 3).

Gestational urinary cadmium concentrations appeared inversely associated with cognitive abilities (full-scale IQ: *B* [95%CI]: −1.1 [−2.5, 0.3] and verbal comprehension: −1.2 [−3.1, 0.6], per doubling; Model 2, Table 3). These adjusted estimates were only marginally lower than the crude estimates (Table 3) and remained about the same when restricted to children whose mothers were non-smokers prior to pregnancy (1). Gestational erythrocyte cadmium concentrations were not associated with cognitive outcomes, especially in the adjusted models, the estimates of which differed markedly from the unadjusted models (Table 3). Children with detectable cord blood erythrocyte cadmium concentrations (>LOD [0.0032 μg/kg], n = 232) had lower full-scale IQ scores compared to children with non-detectable cadmium concentrations (n = 71; *B* [95%CI]: −1.4 [−4.6, 1.7]), but the CIs were wide and the association far from significant (Table 3). Child erythrocyte cadmium concentrations were not associated with the cognitive outcomes, but child urinary cadmium concentrations tended to be inversely associated with cognitive abilities (full-scale IQ: *B* [95%CI]: −1.1 [−2.5, 0.4] and verbal comprehension: *B* [95%CI]: −1.4 [−3.4, 0.6], both per doubling; Model 2, Table 3). The adjusted estimates with child urinary cadmium were markedly increased (almost doubled) compared to the unadjusted model (Table 3). They were also slightly increased in models restricted to children whose mothers were non-smokers prior to pregnancy (Supplemental Table 4), and consistent with the main adjusted models when additionally adjusted for the corresponding gestational or cord blood concentrations (Supplemental Table 5, Model 3 and Model 4, respectively). There was no evidence of modification by child sex in any of the associations (Table 3).

Gestational and child urinary fluoride concentrations were not associated with cognitive outcomes (Table 3, Supplemental Table 6).

3.3. Associations of metal and fluoride exposure with behavioral and social communication problems

Concerning the results of the *CBCL* questionnaire, gestational lead concentrations appeared inversely associated with externalizing problems (*B* [95%CI]: −1.0 [−2.4, 0.3], per doubling; Model 2, Table 4). The estimates did not change when the models were restricted to participants of mothers who did not smoke prior to pregnancy (Supplemental Table 7). Statistically significant interactions by child sex were identified in the association of gestational erythrocyte lead with total and internalizing problems (*P*-for-interaction = 0.040 and 0.047, respectively; Table 4). In stratified models, gestational erythrocyte lead appeared associated with lower total problems in boys (*B* [95%CI]: −1.6 [−3.3, 0.2], girls: 1.4 [−0.6, 3.3], per doubling) and the association was mainly driven by lower externalizing problems (boys: *B* [95%CI]: −2.2 [−4.1, −0.3], girls: 0.4 [−1.5, 2.4], per doubling; Supplemental Table 8), which was also reflected in the main model (Model 2; Table 4). On the other hand, higher internalizing problems were observed in relation to gestational erythrocyte lead in girls (*B* [95%CI]: 2.2 [−0.0, 4.3], boys: −0.9 [−2.8, 1.0], per doubling; Supplemental Table 8). Similarly, erythrocyte lead concentrations in cord blood tended to be associated with increasing internalizing problems (*B* [95%CI]: 1.3 [−0.5, 3.0], per doubling; Table 4), and childhood erythrocyte lead with increasing total problems (*B* [95%CI]: 1.2 [−0.4, 2.9], per doubling), driven mainly by an increase in internalizing problems (1.5 [−0.4, 3.4], per doubling; Model 2, Table 4). The adjusted estimates of childhood lead models were markedly increased (almost doubled) compared to those of the crude models, they were further increased when additionally adjusted for gestational erythrocyte lead concentrations, and consistent with the main models when adjusted for cord blood concentrations (Supplemental Table 9, Model 3 and Model 4, respectively).

Child urinary cadmium concentrations tended to be associated with increased externalizing problems (*B* [95%CI]: 1.1 [−0.2, 2.4], per doubling; Model 2, Table 4). The association did not change when restricted to children of non-smoking mothers (Supplemental Table 7), nor when additionally adjusted for gestational urinary cadmium concentrations or for cord blood concentrations (Supplemental Table 9, Model 3 and Model 4, respectively). The associations of cord blood cadmium concentrations were also positive, but the CIs were wide (Table 4). On the other hand, gestational urinary cadmium and gestational and child erythrocyte cadmium concentrations were not associated with *CBCL* externalizing or internalizing scores (Table 4). In further analyses using the ADHD raw scores of the CBCL, gestational erythrocyte cadmium was associated with slightly increased scores (*B* [95% CI]: 0.3 [−0.0, 0.6], per doubling), while no association was observed with the corresponding urinary cadmium concentrations (Table 5). A significant

Table 3
Multivariate linear regression models of lead, cadmium, and fluoride concentrations in urine and/or erythrocytes of mothers during pregnancy (≈gestational week 29), erythrocyte lead and cadmium concentrations in cord-blood, and lead, cadmium, and fluoride concentrations in urine and/or erythrocytes of children at 4 years of age with cognitive abilities at 4 years of age (full-scale and verbal comprehension scale of *Wechsler Preschool and Primary Scale of Intelligence IV* [*WPPSI-IV*]).

	N	Full scale		*P*-inter.[a]	Verbal scale		*P*-inter.[a]
		B (95% CI)	*P*-value		B (95% CI)	*P*-value	
Lead							
Gestational erythrocyte concentrations (log_2)							
Model 1[b]	439	−1.4 (−3.2, 0.3)	0.105		−1.5 (−3.8, 0.9)	0.216	
Model 2[b]	439	−1.2 (−2.9, 0.5)	0.159	0.927	−1.2 (−3.5, 1.0)	0.282	0.659
Cord blood erythrocyte concentrations (log_2)							
Model 1[b]	303	−1.4 (−3.5, 0.7)	0.180		−1.1 (−3.9, 1.7)	0.443	
Model 2[b]	303	−1.6 (−3.7, 0.4)	0.124	0.392	−1.4 (−4.1, 1.3)	0.318	0.922
Child erythrocyte concentrations (log_2)							
Model 1[b]	249	−0.7 (−2.7, 1.4)	0.519		−0.6 (−3.4, 2.2)	0.671	
Model 2[b]	249	0.2 (−1.9, 2.3)	0.859	0.903	0.5 (−2.3, 3.3)	0.729	0.742
Cadmium							
Gestational urinary concentrations (log_2)[c]							
Model 1[b]	437	−1.2 (−2.6, 0.1)	0.078		−1.4 (−3.3, 0.4)	0.127	
Model 2[b]	437	−1.1 (−2.5, 0.3)	0.130	0.902	−1.2 (−3.1, 0.6)	0.199	0.811
Gestational erythrocyte concentrations (log_2)							
Model 1[b]	439	−1.0 (−2.5, 0.6)	0.221		−1.0 (−3.1, 1.1)	0.338	
Model 2[b]	439	−0.4 (−2.0, 1.2)	0.664	0.890	0.1 (−2.0, 2.2)	0.930	0.884
Cord blood erythrocyte concentrations (above vs below LOD, 0.0032 μg/kg)[d]							
Model 1[b]	303	−1.2 (−4.3, 2.0)	0.476		0.2 (−4.0 4.5)	0.908	
Model 2[b]	303	−1.4 (−4.6, 1.7)	0.373	0.878	−0.3 (−4.4, 3.9)	0.894	0.494
Child urinary concentrations (log_2)[c]							
Model 1[b]	393	−0.6 (−2.2, 0.9)	0.401		−0.8 (−2.8, 1.3)	0.448	
Model 2[b]	393	−1.1 (−2.5, 0.4)	0.163	0.902	−1.4 (−3.4, 0.6)	0.169	0.633
Child erythrocyte concentrations (log_2)							
Model 1[b]	249	0.6 (−1.2, 2.3)	0.526		0.5 (−1.9, 2.9)	0.679	
Model 2[b]	249	0.8 (−0.9, 2.5)	0.356	0.231	0.9 (−1.5, 3.3)	0.460	0.221
Fluoride							
Gestational urinary concentrations (log_2)[c]							
Model 1[b]	425	0.5 (−1.0, 1.9)	0.522		1.1 (−0.8, 3.0)	0.267	
Model 2[b]	425	0.2 (−1.2, 1.6)	0.799	0.582	0.4 (−1.4, 2.3)	0.641	0.668
Child urinary concentrations (log_2)[c]							
Model 1[b]	392	−0.3 (−1.6, 1.0)	0.620		−0.3 (−2.1, 1.4)	0.705	
Model 2[b]	392	−0.3 (−1.6, 0.9)	0.596	0.979	−0.4 (−2.1, 1.4)	0.678	0.218

[a] P-value for interaction with child sex (male/female).
[b] Model 1 presents crude associations and Model 2 is adjusted for maternal age (continuous; years), maternal education (categorical; no university degree or university degree), parity (categorical; primiparous or multiparous), maternal smoking before pregnancy (categorical; no or yes), child sex (categorical; boy or girl), and child age at assessment (continuous; months).
[c] Urinary cadmium and fluoride concentrations are adjusted to median specific gravity (1.017 for the mothers and 1.016 for the children).
[d] Above the limit of detection (LOD; n = 232) vs below LOD (n = 71).

interaction by child sex was identified in the association of gestational erythrocyte cadmium and ADHD problems (*P*-for-interaction = 0.021; Table 5). When analyses were stratified by sex, cadmium was associated with increased ADHD problems in girls (*B* [95% CI]: 0.5 [0.0, 0.9] per doubling), whereas no association was observed in boys (*B* [95% CI]: −0.1 [−0.5, 0.4] per doubling) (Supplemental Table 8).

Urinary fluoride concentrations were not associated with *CBCL* scores (Table 4 & Supplemental Table 10), except for a potential association of gestational urinary fluoride concentrations with increasing externalizing problems *B* [CI 95% CI]: 0.9 [−0.3, 2.0]), per doubling (Table 4). Additional analyses using the ADHD scale of the *CBCL* showed an association of gestational urinary fluoride concentrations with slightly higher ADHD raw scores (*B* [CI 95% CI]: 0.3 [0.0, 0.6], per doubling, Table 5; *B* [CI 95% CI]: 0.1 [−0.0, 0.3], per 0.5 mg/L increase, Supplemental Table 11). The *SRS-2* total score appeared unrelated to cadmium, lead, and fluoride exposure (Table 6 & Supplemental Table 12). Child sex did not modify the association between lead, cadmium, and fluoride and SRS-2 outcomes in any meaningful or consistent way (Table 6).

4. Discussion

Prenatal exposure to lead in the Swedish NICE cohort was associated with lower cognitive abilities at 4 years of age. More importantly given the limited number of previous studies, the results reinforce that also low-level cadmium exposure during pregnancy and early childhood may be associated with lower child cognitive abilities. Both lead and cadmium associations remained stable when adjusted for potential confounders, although they were statistically non-significant. The associations of lead and cadmium with behavioral problems were less consistent. Gestational fluoride exposure was associated with externalizing problems, including ADHD, but prevalence of behavioral problems was low, causing major uncertainty.

It is well-established that even low-level early-life lead exposure causes developmental neurotoxicity (Crump et al., 2013; Lanphear et al., 2005). In the recent health risk assessment, a benchmark dose lower limit (BMDL) value of 12 μg/L was estimated based on childhood blood lead levels (EFSA, 2010). We found no cross-sectional association between child erythrocyte lead concentrations (median: 6 μg/kg) and cognitive abilities at 4 years of age; however, an inverse association was suggested between gestational erythrocyte lead concentrations at gestational week 29 (median: 11.2 μg/kg; corresponding to approximately 4.4 μg/L in whole blood) and child full-scale and verbal IQ. This was supported by similar associations in the models based on erythrocyte lead concentrations in cord blood (median: 7.8 μg/kg). These findings are in line with several previous studies on prenatal lead exposure and child cognition, most of which measured the prenatal exposure by lead concentrations in cord blood (Bellinger et al., 1987;

Table 4
Multivariate linear regression models of lead, cadmium, and fluoride concentrations in urine and/or erythrocytes of mothers during pregnancy (≈gestational week 29), lead and cadmium concentrations in cord-blood erythrocytes, and lead, cadmium, and fluoride concentrations in urine and/or erythrocytes of children at 4 years of age with parental-evaluated behavioural problems at 4 years of age (*Child Behaviour Checklist* [*CBCL*]).

	N	Total problems			Externalizing problems			Internalizing problems		
		B (95% CI)	*P*-value	*P*-inter.[a]	B (95% CI)	*P*-value	*P*-inter.[a]	B (95% CI)	*P* value	*P*-inter.[a]
Lead										
Gestational erythrocyte concentrations (log_2)										
Model 1[b]	352	−0.4 (−1.8, 1.0)	0.565		−1.2 (−2.6, 0.2)	0.096		0.4 (−1.1, 1.9)	0.570	
Model 2[b]	352	−0.2 (−1.5, 1.1)	0.748	0.040	−1.0 (−2.4, 0.3)	0.140	0.086	0.6 (−0.8, 2.1)	0.400	0.047
Cord blood erythrocyte concentrations (log_2)										
Model 1[b]	248	0.5 (−1.2, 2.2)	0.548		0.0 (−1.7, 1.8)	0.972		1.2 (−0.6, 3.0)	0.202	
Model 2[b]	248	0.6 (−1.0, 2.2)	0.430	0.373	0.2 (−1.4, 1.9)	0.784	0.942	1.3 (−0.5, 3.0)	0.153	0.050
Child erythrocyte lead concentrations (log_2)										
Model 1[b]	191	0.5 (−1.2, 2.3)	0.540		0.4 (−1.5, 2.3)	0.655		0.7 (−1.2, 2.6)	0.481	
Model 2[b]	191	1.2 (−0.4, 2.9)	0.146	0.300	0.9 (−0.9, 2.7)	0.336	0.479	1.5 (−0.4, 3.4)	0.127	0.342
Cadmium										
Gestational urinary concentrations (log_2)[c]										
Model 1[b]	350	−0.1 (−1.3, 1.0)	0.793		−0.3 (−1.5, 0.9)	0.605		−0.2 (−1.5, 1.0)	0.718	
Model 2[b]	350	0.0 (−1.1, 1.1)	0.964	0.323	0.0 (−1.1, 1.2)	0.964	0.323	−0.2 (−1.5, 1.0)	0.709	0.263
Gestational erythrocyte concentrations (log_2)										
Model 1[b]	352	0.9 (−0.3, 2.1)	0.161		0.7 (−0.5, 2.0)	0.246		0.4 (−1.0, 1.7)	0.604	
Model 2[b]	352	0.4 (−0.8, 1.7)	0.478	0.167	0.4 (−0.9, 1.7)	0.508	0.034	−0.3 (−1.7, 1.0)	0.632	0.809
Cord blood erythrocyte concentrations (above vs below LOD, 0.0032 μg/kg)[d]										
Model 1[b]	248	1.2 (−1.3, 3.8)	0.341		0.9 (−1.7, 3.5)	0.506		0.2 (−2.6, 3.0)	0.907	
Model 2[b]	248	1.5 (−1.0, 4.0)	0.230	0.519	1.4 (−1.2, 4.0)	0.283	0.325	0.2 (−2.5, 3.0)	0.865	0.848
Child urinary concentrations (log_2)[c]										
Model 1[b]	310	0.8 (−0.5, 2.1)	0.238		1.2 (−0.2, 2.5)	0.084		0.4 (−1.0, 1.8)	0.565	
Model 2[b]	310	0.6 (−0.6, 1.8)	0.350	0.124	1.1 (−0.2, 2.4)	0.107	0.480	0.1 (−1.2, 1.5)	0.826	0.183
Child erythrocyte concentrations (log_2)										
Model 1[b]	191	0.5 (−1.0, 2.1)	0.488		0.4 (−1.3, 2.1)	0.633		0.6 (−1.1, 2.3)	0.473	
Model 2[b]	191	0.6 (−0.8, 2.1)	0.394	0.866	0.4 (−1.2, 2.0)	0.593	0.592	0.7 (−0.9, 2.4)	0.388	0.882
Fluoride										
Gestational urinary concentrations (log_2)[c]										
Model 1[b]	341	0.3 (−0.8, 1.4)	0.616		0.6 (−0.5, 1.8)	0.275		0.4 (−0.8, 1.6)	0.521	
Model 2[b]	341	0.4 (−0.7, 1.5)	0.493	0.200	0.9 (−0.3, 2.0)	0.132	0.139	0.4 (−0.8, 1.6)	0.466	0.596
Child urinary concentrations (log_2)[c]										
Model 1[b]	310	0.1 (−1.0, 1.1)	0.918		0.4 (−0.8, 1.5)	0.526		0.2 (−0.9, 1.4)	0.690	
Model 2[b]	310	−0.1 (−1.1, 0.9)	0.854	0.399	0.3 (−0.8, 1.3)	0.628	0.754	0.1 (−1.0, 1.2)	0.900	0.882

[a] P-value for interaction with child sex (male/female).
[b] Model 1 presents crude associations and Model 2 is adjusted for maternal age (continuous; years), maternal education (categorical; no university degree or university degree), parity (categorical; primiparous or multiparous), maternal smoking before pregnancy (categorical; no or yes), child sex (categorical; boy or girl), and child age at assessment (continuous; months).
[c] Urinary cadmium and fluoride concentrations are adjusted to median specific gravity (1.017 for the mothers and 1.016 for the children).
[d] Above the limit of detection (LOD; n = 190) vs below LOD (n = 58).

Garí et al., 2022; Kordas et al., 2011; Yorifuji et al., 2011). Unexpectedly gestational erythrocyte lead concentrations were associated with decreasing externalizing problems in boys, but given that this association is biologically implausible, it is likely due to residual confounding. One possible explanation is that, in the NICE study, mothers with higher lead concentrations more frequently lived in more rural areas where outdoor life and hunting are common parts of peoples' lifestyle, as suggested by the previously shown correlation between maternal erythrocyte lead levels and game-meat intake (Gustin et al., 2020) and such a lifestyle could be more accepting of externalizing problems, which then would be rated lower. This explanation aligns with our previous findings, which also suggested an unexpected association of gestational erythrocyte lead concentrations with lower odds of allergy in infancy, likely due to similar residual confounding related to lifestyle (Kampouri et al., 2023). Both gestational and cord blood erythrocyte lead were associated with higher internalizing problems in girls only, which aligns with findings from previous studies indicating higher sensitivity to lead among girls regarding internalizing problems (Burns et al., 1999; Fruh et al., 2019). Lead concentrations at 4 years of age appeared to be cross-sectionally associated with increased behavioral problems, consistent with findings from gestational and cord blood lead concentrations but without any indication of sex interaction in the associations. Our findings agree with previous studies reporting links of lead exposure to various behavioral problems in children and adolescents (Bellinger et al., 1994; Bellinger, 2008; Donzelli et al., 2019; Fruh et al., 2019).

The indicated association of gestational cadmium exposure with lower child cognitive abilities aligns with findings from previous prospective studies conducted in Greece (Kippler et al., 2016) and Bangladesh (Kippler et al., 2012), both of which reported inverse associations of maternal urinary cadmium concentrations in pregnancy (median: 0.43 μg/L and 0.63 μg/L, respectively) with cognitive abilities at preschool age. Taken together, cadmium appears to impair child cognition in populations with different exposure levels, irrespective of the source or route of exposure (*i.e.,* tobacco smoking and certain food), as well as with differences in cognitive development. Interestingly, gestational and childhood urinary cadmium concentrations (median: 0.10 μg/L and 0.04 μg/L, respectively), reflective of long-term exposure (Järup and Åkesson, 2009), showed much stronger associations with child cognition than did the erythrocyte concentrations (median: 0.29 μg/kg and 0.15 μg/L, respectively]), which reflect exposure during the last few months. In agreement with findings from a Korean study, which identified significant associations between whole blood cadmium and ADHD scores in 6-year-old girls (Kim et al., 2020), gestational erythrocyte cadmium concentrations were associated with ADHD problems in girls. However, no such association was observed with urinary cadmium concentrations, which reflect long-term cadmium exposure; therefore, this finding is uncertain. In addition, the variation in the ADHD scale in

Table 5
Multivariate linear regression models of lead, cadmium, and fluoride concentrations in urine and/or erythrocytes of mothers during pregnancy (≈gestational week 29), lead and cadmium concentrations in cord-blood erythrocytes, and lead, cadmium, and fluoride concentrations in urine and/or erythrocytes of children at 4 years of age with raw scores of parental-evaluated attention-deficit-hyperactivity problems at 4 years of age (*Child Behaviour Checklist* [*CBCL*]).

	ADHD problems			
	N	B (95% CI)	*P*-value	*P*-inter.[a]
Lead				
Gestational erythrocyte concentrations (log_2)				
Model 1[b]	352	−0.3 (−0.6, 0.1)	0.125	
Model 2[b]	352	−0.2 (−0.5, 0.1)	0.174	0.873
Cord blood erythrocyte concentrations (log_2)				
Model 1[b]	248	0.0 (−0.4, 0.4)	0.959	
Model 2[b]	248	0.0 (−0.4, 0.4)	0.888	0.459
Child erythrocyte concentrations (log_2)				
Model 1[b]	191	0.1 (−0.3, 0.5)	0.613	
Model 2[b]	191	0.2 (−0.2, 0.7)	0.272	0.737
Cadmium				
Gestational urinary concentrations (log_2)[c]				
Model 1[b]	350	0.1 (−0.2, 0.3)	0.588	
Model 2[b]	350	0.1 (−0.2, 0.4)	0.410	0.824
Gestational erythrocyte concentrations (log_2)				
Model 1[b]	352	0.3 (0.0, 0.6)	0.023	
Model 2[b]	352	0.3 (−0.0, 0.6)	0.093	0.021
Cord blood erythrocyte concentrations (above vs below LOD, 0.0032 μg/kg)[d]				
Model 1[b]	248	−0.1 (−0.7, 0.5)	0.707	
Model 2[b]	248	−0.1 (−0.7, 0.6)	0.860	0.918
Child urinary concentrations (log_2)[c]				
Model 1[b]	310	0.3 (−0.0, 0.6)	0.062	
Model 2[b]	310	0.2 (−0.1, 0.5)	0.105	0.621
Child erythrocyte concentrations (log_2)				
Model 1[b]	191	0.2 (−0.1, 0.6)	0.228	
Model 2[b]	191	0.2 (−0.1, 0.6)	0.191	0.232
Fluoride				
Gestational urinary concentrations (log_2)[c]				
Model 1[b]	341	0.3 (0.0, 0.6)	0.042	
Model 2[b]	341	0.3 (0.0, 0.6)	0.020	0.419
Child urinary concentrations (log_2)[c]				
Model 1[b]	310	0.1 (−0.1, 0.4)	0.396	
Model 2[b]	310	0.1 (−0.2, 0.3)	0.509	0.589

[a] P-value for interaction with child sex (male/female).
[b] Model 1 presents crude associations and Model 2 is adjusted for maternal age (continuous; years), maternal education (categorical; no university degree or university degree), parity (categorical; primiparous or multiparous), maternal smoking before pregnancy (categorical; no or yes), child sex (categorical; boy or girl), and child age at assessment (continuous; months).
[c] Urinary cadmium and fluoride concentrations are adjusted to median specific gravity (1.017 for the mothers and 1.016 for the children).
[d] Above the limit of detection (LOD; n = 190) vs below LOD (n = 58).

the present study is limited with scores being on average low (5th-95th percentile: 0–6 raw scores and only 3 participants would be classified borderline/clinical based on the corresponding T-score cut-offs), increasing the possibility of a chance finding.

The indicated inverse associations between long-term childhood cadmium exposure and cognition are consistent with findings from cross-sectional analyses conducted in 5-year and 10-year-old Bangladeshi children (Gustin et al., 2018; Kippler et al., 2012), in 6–9 year-old Spanish children (Rodríguez-Barranco et al., 2014), and in 2.5-year-old Chinese children (Liu et al., 2022). An American study also demonstrated inverse associations between cadmium exposure (blood concentrations) measured at 2 years of age and cognitive abilities at ages 5 and 7 years, although the estimates did not reach statistical significance (Cao et al., 2009). In the latter study, and in agreement with the present results, associations of child cadmium exposure measured at 2 years and behavioral problems at 5 and 7 years were also shown, although these associations were also statistically non-significant (Cao et al., 2009).

The mechanisms of cadmium-induced neurodevelopmental toxicity following gestational and childhood exposure may differ, as very little cadmium passes the placenta (Kippler et al., 2010; Osman et al., 2000), corroborated by the very low concentrations in cord blood observed in the present study. Indirect cadmium-induced neurodevelopmental effects are possible, especially in the prenatal period, during which the accumulation of cadmium in the placenta may cause toxicity, resulting in e.g., impaired transfer of micronutrients crucial for fetal neurodevelopment (Kippler et al., 2010) and altered DNA methylation leading to epigenetic changes that influence fetal programming (Vilahur et al., 2015). Furthermore, cadmium may impact thyroid hormones (Gustin et al., 2021; Margetaki et al., 2021), which are implicated in neurodevelopmental processes starting shortly after conception and unfolding throughout childhood and adolescence (Williams, 2008). Cadmium can also damage the blood-brain barrier via effects on tight junctions and is transported into the central nervous system via zinc and calcium transporters, where it may cause oxidative stress and mitochondrial disruption, changes in neurotransmitter signaling, and altered glycogen metabolism (Arruebarrena et al., 2023). These direct modes of action are particularly relevant for postnatal cadmium exposure.

Over the last 5 years, prospective studies in populations exposed to low-levels of fluoride in Canada (MIREC study) and Mexico (ELEMENT study) have reported reductions in cognitive development in relation to maternal urinary fluoride concentrations during pregnancy (Bashash et al., 2017; Farmus et al., 2021; Goodman et al., 2022; Green et al., 2019). Based on the combined individual data from the two cohorts and a recent Danish cohort (OCC study), a urinary fluoride concentration of 0.3 mg/L was considered to correspond to the benchmark concentration level leading to a 1-point IQ reduction (Grandjean et al., 2022, 2024). The present urinary fluoride concentrations were comparable with the those reported in the aforementioned prospective studies (NICE study:

Table 6
Multivariate linear regression models of lead, cadmium, and fluoride concentrations in urine and/or erythrocytes of mothers during pregnancy (≈gestational week 29), lead and cadmium concentrations in cord-blood erythrocytes, and lead, cadmium, and fluoride concentrations in urine and/or erythrocytes of children at 4 years of age with parental-evaluated social communication problems at 4 years of age (*Social Responsiveness Scale-2* [*SRS-2*]).

	Total scale			
	N	B (95% CI)	*P*-value	*P*-inter.[a]
Lead				
Gestational erythrocyte concentrations (log_2)				
Model 1[b]	388	−0.3 (−1.1, 0.6)	0.556	
Model 2[b]	388	−0.3 (−1.1, 0.5)	0.494	0.854
Cord blood erythrocyte concentrations (log_2)				
Model 1[b]	268	0.1 (−1.0, 1.1)	0.912	
Model 2[b]	268	0.0 (−1.0, 1.1)	0.974	0.504
Child erythrocyte concentrations (log_2)				
Model 1[b]	209	0.2 (−0.8, 1.3)	0.685	
Model 2[b]	209	0.3 (−0.8, 1.4)	0.565	0.065
Cadmium				
Gestational urinary concentrations (log_2)[c]				
Model 1[b]	386	−0.0 (−0.7, 0.7)	0.967	
Model 2[b]	386	0.0 (−0.7, 0.7)	0.911	0.273
Gestational erythrocyte concentrations (log_2)				
Model 1[b]	388	0.4 (−0.4, 1.2)	0.320	
Model 2[b]	388	0.2 (−0.6, 1.0)	0.592	0.062
Cord blood erythrocyte concentrations (above vs below LOD, 0.0032 μg/kg)[d]				
Model 1[b]	268	1.1 (−0.5, 2.6)	0.181	
Model 2[b]	268	1.3 (−0.3, 2.8)	0.112	0.594
Child urinary concentrations (log_2)[c]				
Model 1[b]	342	−0.0 (−0.8, 0.8)	0.972	
Model 2[b]	342	−0.0 (−0.8, 0.8)	0.928	0.587
Child erythrocyte concentrations (log_2)				
Model 1[b]	209	0.7 (−0.3, 1.6)	0.187	
Model 2[b]	209	0.6 (−0.4, 1.6)	0.212	0.904
Fluoride				
Gestational urinary concentrations (log_2)[c]				
Model 1[b]	375	0.1 (−0.5, 0.8)	0.684	
Model 2[b]	375	0.2 (−0.5, 0.9)	0.513	0.108
Child urinary concentrations (log_2)[c]				
Model 1[b]	341	−0.2 (−0.8, 0.5)	0.642	
Model 2[b]	341	−0.2 (−0.9, 0.5)	0.549	0.254

[a] P-value for interaction with child sex (male/female).
[b] Model 1 presents crude associations and Model 2 is adjusted for maternal age (continuous; years), maternal education (categorical; no university degree or university degree), parity (categorical; primiparous or multiparous), maternal smoking before pregnancy (categorical; no or yes), child sex (categorical; boy or girl), and child age at assessment (continuous; months).
[c] Urinary cadmium and fluoride concentrations are adjusted to median specific gravity (1.017 for the mothers and 1.016 for the children).
[d] Above the limit of detection (LOD; n = 201) vs below LOD (n = 67).

median [range]: 0.7 mg/L [0.06–6.4]); MIREC study: median [range]: 0.41 mg/L [0.06–2.44]; ELEMENT study: mean [range]: 0.90 mg/L [0.23, 2.36]), but we did not observe any association with full-scale or verbal IQ. However, we did not assess performance ability, which has been identified as the most sensitive cognitive domain to fluoride exposure from the two previous prospective studies in Canada and Mexico (Farmus et al., 2021; Goodman et al., 2022). To note, the OCC cohort study showed no association of maternal urinary fluoride concentrations in late pregnancy (median 0.5, range 0.08–3.0 mg/L) with full-scale intelligence at 7 years of age (Grandjean et al., 2024). With regards to behavioral outcomes, gestational urinary fluoride concentrations were associated with a small increase in externalizing problems and in ADHD problems. This is in agreement with previous findings reported from the ELEMENT study with a more comprehensive assessment of ADHD (Bashash et al., 2018) and from a small recent study in the United States (Malin et al., 2024), which both indicated a potential link with ADHD problems, although in the latter study the exposure assessment was uncertain and the association was not statistically significant.

The main strengths of the present study include the prospective design and the use of appropriate biomarkers to assess cadmium, lead, and fluoride exposure from all sources. Urinary cadmium reflects long-term exposure, while fluoride concentrations in spot urine samples reflect recent fluoride intake from all sources. It is noteworthy that exposure misclassification due to relying on a single spot urine sample and gestational-age dependent variability in fluoride urinary excretion, may have biased our results towards null. However, most women provided a urine sample within a relatively narrow range of gestational weeks. Cognitive and behavioral assessment utilized established and sound psychometric instruments covering various domains (*i.e.,* cognitive development, behavioral problems, social communication). However, cognitive development testing focused on assessment of full-scale intelligence and verbal comprehension and we did not assess the potential impact on other cognitive domains, which may have been affected, especially by fluoride. Additionally, we lacked data on parental intelligence and stimulation at home (*i.e.,* home observation for measurement of the environment [HOME]) that could have enhanced the predictive capacity of the models, thereby strengthening the observed associations. Concerning the generalizability of the findings, we acknowledge that the pregnant women in the NICE cohort differed somewhat in background and lifestyle characteristics, including age, educational level, cohabitation with a partner, smoking status, and supplement use during pregnancy, compared to pregnant women residing in the study area in northern Sweden, but did not participate in the NICE cohort (Ögge et al., 2022). Finally, as in all observational studies, we cannot exclude residual confounding.

In conclusion, the present results, taken together with results of previous studies, suggest that low-level cadmium exposure in pregnancy

or early childhood may lead to lower cognitive abilities at 4 years of age. More expected, prenatal lead exposure appeared to be linked to lower cognitive abilities. The associations of cadmium with child behavioral problems were inconsistent and statistically uncertain, whereas the associations of lead and fluoride were indicative of increasing behavioral problems. Additional large-scale prospective studies in different populations, as well as mechanistic studies are needed to increase our understanding of the impact of cadmium and fluoride on child neurodevelopment. Even small adverse effects of these very common exposures constitute significant public health problems.

CRediT authorship contribution statement

Mariza Kampouri: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis. **Eric Zander:** Writing – review & editing, Methodology, Data curation. **Klara Gustin:** Writing – review & editing, Data curation. **Anna Sandin:** Writing – review & editing, Funding acquisition. **Malin Barman:** Writing – review & editing. **Ann-Sofie Sandberg:** Writing – review & editing, Funding acquisition. **Agnes E. Wold:** Writing – review & editing, Funding acquisition. **Sven Bölte:** Writing – review & editing, Methodology. **Maria Kippler:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. **Marie Vahter:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

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 data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.120123.

Data availability

The data that has been used is confidential.

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