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Associations of gestational and early-life exposure to toxic metals and fluoride with a diagnosis of food allergy or atopic eczema at 1 year of age

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ABSTRACT

Studies have indicated that early-life exposure to toxic metals and fluoride affects the immune system, but evidence regarding their role in allergic disease development is scarce. We aimed to evaluate the relations of exposure to such compounds in 482 pregnant women and their infants (4 months of age) with food allergy and atopic eczema diagnosed by a paediatric allergologist at 1 year of age within the Swedish birth-cohort NICE (Nutritional impact on Immunological maturation during Childhood in relation to the Environment). Urinary cadmium and erythrocyte cadmium, lead, and mercury concentrations were measured by inductively coupled plasma mass spectrometry (ICP-MS), urinary inorganic arsenic metabolites by ICP-MS after separation by ion exchange chromatography, and urinary fluoride by an ion-selective electrode. The prevalence of food allergy and atopic eczema was 8 and 7%, respectively. Gestational urinary cadmium, reflecting chronic exposure, was associated with increased odds of infant food allergy (OR [95% CI]: 1.34 [1.09, 1.66] per IQR [0.08 μg/L]). Both gestational and infant urinary fluoride were associated, albeit at a statistically non-significant level, with increased atopic eczema odds (1.48 [0.98, 2.25], 1.36 [0.95, 1.95], per doubling, respectively). By contrast, gestational and infant erythrocyte lead was associated with decreased odds of atopic eczema (0.48 [0.26, 0.87] per IQR [6.6 μg/kg] and 0.38 [0.16, 0.91] per IQR [5.94 μg/kg], respectively), and infant lead with decreased odds of food allergy (0.39 [0.16, 0.93] per IQR [5.94 μg/kg]). Multivariable adjustment had marginal impact on the estimates above. After additional adjustment for fish intake biomarkers, the methylmercury associated atopic-eczema odds were considerably increased (1.29 [0.80, 2.06] per IQR [1.36 μg/kg]). In conclusion, our results indicate that gestational cadmium exposure might be associated with food allergy at 1 year of age and, possibly, early-life exposure to fluoride with atopic eczema. Further prospective and mechanistic studies are needed to establish causality.

1. Introduction

Atopic and allergic diseases, such as food allergy, atopic eczema, asthma, and allergic rhinitis, are the most common chronic conditions of childhood, affecting more than 20% of the global population (World Health Organization, 2003). Food allergy and atopic eczema may appear already in the first year of life, while asthma and allergic rhinitis usually have a later onset. The atopic diseases frequently coexist with food allergy, e.g., food allergy is connected to atopic eczema, especially of a severe, persistent, and early-onset type (Bantz et al., 2014). Further, atopic diseases may follow one another during the life span, e.g., atopic eczema may wane and be replaced by asthma and allergic rhinitis, a phenomenon termed "the atopic march" (Spergel and Paller, 2003).

The aetiology of allergies involves interactions between genetic factors and lifestyle and/or environmental exposures. Early life is a period of programming of the immune system and exposure to specific foods, microbes, and chemicals may affect this programming, and hence the chance of developing physiological tolerance or, conversely, allergy to harmless environmental antigens, "allergens" (Dietert, 2014).

Early-life exposure to toxic metals has been associated with various

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adverse developmental outcomes (Quansah et al., 2015; Sanders et al., 2015; Vrijheid et al., 2016). Recent studies also suggest that exposure to toxic metals, including the metalloid arsenic, during the fetal period (Ahmed et al., 2012; Nadeau et al., 2014; Nygaard et al., 2017; Raqib et al., 2017) or childhood (Ahmed et al., 2014; Raqib et al., 2017; Wells et al., 2014) may dysregulate the function of the immune system (i.e., influencing the distribution of T-cell subpopulations and increasing immunoglobulin E levels). However, studies on the potential impact of metal exposure on the risk of allergy are limited in number (Vrijheid et al., 2016). A few birth cohort studies have suggested that there are increased odds of atopic eczema related to lead exposure (Kim et al., 2016; Lee et al., 2021), of allergic rhinitis and asthma related to arsenic exposure (Ruan et al., 2022; Tsai et al., 2021), of food allergy and/or atopic eczema related to cadmium exposure (Kim et al., 2013; Pesce et al., 2021) and of atopic eczema related to mercury exposure (Kim et al., 2016). However, the above specified associations were not identified in all studies (Kim et al., 2019; Kim et al., 2013; Miyake et al., 2011; Pesce et al., 2021). In addition, fluoride exposure (a non-metallic element belonging to the halogens) has been linked with immune-system alterations in *in-vitro* studies (De la Fuente et al., 2016; Ma et al., 2016; Ma et al., 2017; Shi et al., 2016), but epidemiological data on its possible role in allergic disease are lacking. In the present study, we aimed to investigate whether early-life low-level exposure to cadmium, lead, mercury, arsenic, or fluoride measured by concentrations in maternal erythrocyte and/or urine during gestation or in infant erythrocyte and urine concentrations at 4 months of age, was associated with food allergy or atopic eczema at 1 year of age.

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 study in northern Sweden (Barman et al., 2018). The NICE study was established in the Norrbotten county between 2015 and 2018, and it was set up to assess the influence of early-life environment, primarily on immune maturation and allergy development as well as on growth, neurodevelopment, and oral health. Expecting parents received an information leaflet during their visit to the local maternity clinics. Then, at the routine ultrasound around gestational week 18, if they expressed interest in participation, they were informed in detail about the study and received a written participation consent to sign at home and to return by post. The inclusion criteria for participation in the study were to be residents in the Norrbotten region, planning to give birth at Sunderby Hospital, and being able to communicate in Swedish.

From a total of 655 pregnancies that were enrolled in NICE, families already participating with a previous birth, twin pregnancies, miscarriages, stillbirths, and one participant who withdrew the consent were excluded (Supplemental Figure S1). Out of the remaining 629 mother-infant pairs, erythrocyte samples were available from 591 pregnant women, and adequate volume of collected urinary samples to measure cadmium, fluoride, and inorganic arsenic metabolites (by different methods) was available from 588, 568, 583 pregnant women, respectively. Erythrocyte and urine samples at 4 months of age were available from 229 and 356 infants, respectively. Out of those with gestational exposure data, data on allergic disease and complete covariate data (< 5% missing) was available from 482 mother–child dyads in the analyses of maternal erythrocyte metal concentrations, and 481, 467, and 477 dyads in the analyses of maternal urinary cadmium, fluoride, inorganic arsenic, respectively. For infants, 210 and 321 remained in the analyses of erythrocyte metals and urinary fluoride at 4 months of age, respectively.

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

2.2. Sample collection

Blood and spot urine samples were collected at the local maternity clinics at approximately gestational week 29 (Barman et al., 2018; Gustin et al., 2021; Gustin et al., 2020) and at 4 months of age at the hospital. Blood samples for metal analyses 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 kept in the collection tube and stored at -20 °C or below until transported frozen to Karolinska Institutet, Sweden, for trace element analyses.

2.3. Exposure assessment

Maternal exposure to cadmium during pregnancy was assessed by concentrations in erythrocytes, reflecting exposure during the last few months, and in urine, reflecting chronic exposure (Akerstrom et al., 2013). Exposure to lead and mercury was assessed by concentrations in erythrocytes, both representing exposure during the last few months (Neve, 1995). Erythrocyte mercury is a suitable biomarker of methylmercury exposure (Berglund et al., 2005). Exposure to inorganic arsenic was assessed by the concentrations of its metabolites in urine [sum of inorganic arsenic (iAs), methylarsonic acid (MMA), and dimethylarsinic acid (DMA)], reflecting ongoing exposure (Vahter, 2002). Also, exposure to fluoride was measured by the concentration in urine, which reflects contemporary exposure (Whitford, 1994). Infant exposures were assessed by concentrations of cadmium, lead, and mercury in erythrocytes and of fluoride in urine collected at 4 months of age. We did not speciate arsenic metabolites in infant urine as most infants were exclusively breastfed resulting in very low transfer of inorganic arsenic (Fängström et al., 2008).

Metal concentrations in erythrocytes and urine were measured with inductively coupled plasma mass spectrometry (ICP-MS; Agilent 7700x and 7900, Agilent Technologies, Tokyo, Japan), equipped with an octopole reaction system (Gustin et al., 2020). Inorganic arsenic metabolites in urine were first separated by ion exchange chromatography (Vahter et al., 2020). 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 limit of detection (LOD) was 0.0037 μg/kg, 0.11 μg/kg, and 0.01 μg/kg for maternal erythrocyte cadmium, lead, and mercury, respectively (Gustin et al., 2020). The LOD value for maternal urinary cadmium was 0.003 μg/L (Gustin et al., 2020). The LOD values for inorganic arsenic metabolites (calculated as 3 times the standard deviation of the blank concentration), i.e., AsV (AsIII was oxidized to AsV before the separation), MMA, and DMA were 0.089 μg/L, 0.11 μg/L, and 0.049 μg/L, respectively. The LOD for urinary fluoride was 0.05 mg/L (Kampouri et al., 2022). Two maternal erythrocyte samples had a mercury concentration below the LOD, and they were replaced by LOD divided by the square root of 2, and two maternal urine samples had fluoride concentrations below the LOD, and their concentrations were kept as measured since they had positive values (Helsel, 1990). The LOD values for cadmium, lead, and mercury in infant erythrocytes were 0.07 μg/kg, 0.045 μg/kg, and 0.017 μg/kg, respectively. The LOD for fluoride in infant urine 0.01 mg/L. Eleven infant erythrocyte samples had a mercury concentration below the LOD and were replaced with LOD divided by the square root of 2, whereas the nine infant urine samples having a fluoride concentration below the LOD were retained in the

dataset since they still had positive values. More than 60% of the infant samples had cadmium concentrations below the LOD. Thus, we did not evaluate the infant cadmium-outcome associations. The quality control of the analyses of the maternal exposure biomarkers have been presented in detail (Gustin et al., 2020; Kampouri et al., 2022; Stråvik et al., 2023), and quality control of the analyses of the infant exposure biomarkers are presented in Supplemental Table S1.

Urine samples were adjusted for specific gravity to control the urinary concentrations for the variation in urine dilution. Specific gravity was measured with a digital refractometer (EUROMEX RD712, Clinical Refractometer, Holland), and all urinary concentrations were adjusted to the mean specific gravity (maternal urine: mean = 1.017, infant urine: mean = 1.004) applying the following formula: adjusted urinary concentration = unadjusted urinary concentration×(specific gravity$_{mean}$-1)/(specific gravity$_{sample}$-1).

2.4. Outcome assessment

Atopic and allergic diseases were diagnosed at 1 year of age by a paediatrician with expertise in allergology, using standard protocols (Stråvik et al., 2020). Food allergy was defined as a reaction to the intake of a specific food along with an improvement of the clinical symptoms once the food was removed from the diet. Oral provocation was performed, except for cases of very severe reactions, and the type of food allergy has been determined (Stråvik et al., 2020). Atopic eczema was diagnosed according to Williams' criteria (Williams et al., 1994a; Williams et al., 1994b; Williams et al., 1994c).

2.5. Covariates

Information on maternal age (years), early-pregnancy body mass index [BMI (kg/m^2)], parity (number of previous births), education (elementary school, high school, or university), smoking prior to pregnancy (never, sometimes, or daily), birth weight (kg), gestational age at delivery (gestational week), infant sex (male, female), and date of birth was obtained from the hospital records. We used smoking data before pregnancy instead of smoking during pregnancy, since only a few women smoked during pregnancy (n = 4). Information on the history of allergic disease in the family, defined as parents or siblings with atopic eczema, food allergy, allergic rhinoconjunctivitis, or asthma, was collected from the parents at the 1-year follow-up assessment with a structured interview conducted by a paediatrician with allergy specialization. Information on pet ownership (yes, no) was collected during pregnancy through a questionnaire, and breastfeeding information (no, partially, exclusively) was collected using monthly questionnaires sent out during the first year of life. In the models of erythrocyte mercury, reflecting exposure to methylmercury (Berglund, 2005), we also adjusted for two biomarkers of fish and seafood intake; i) n-3 long-chain polyunsaturated fatty acids (n-3 LCPUFAs; mainly reflecting fatty fish intake) measured in maternal and infant erythrocyte phospholipid fraction in samples collected at gestational week 29 and at 4 months of age, respectively (Barman et al., 2021), and ii) maternal and infant erythrocyte total arsenic concentrations, which have been shown to mainly reflect arsenobetaine, derived from seafood intake (Stråvik et al., 2023).

2.6. Statistical analyses

Statistical analyses were performed using the software Stata/IC 15.0 (StataCorp, TX, USA). P-values below 0.05 were considered statistically significant, but we also considered the consistency and robustness of the results. Bivariate correlations between the exposure biomarkers (erythrocyte concentrations of cadmium, lead, and mercury, and urinary concentrations of arsenic metabolites, cadmium, and fluoride), the allergy outcomes (food allergy, atopic eczema) 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 created using DAGitty version 3.0 based on previous knowledge of the data structure to facilitate the selection of the minimal sufficient adjustment set for logistic regression analyses (Supplemental Figure S2). The minimally adjusted models included allergy history in the family (parents or siblings with allergy; yes or no) and infant sex (male or female), which were both a priori selected adjustment factors. The fully adjusted models included maternal age (continuous; years), maternal education (categorical; no university degree or university degree), maternal BMI (continuous; kg/m^2), parity (categorical; primiparous or multiparous), maternal smoking (categorical; no or yes), pet ownership (categorical; no or yes), and the season of birth [categorical; dark season (October to March) or bright season (April to September)], based on the DAG structure.

Generalized additive models (GAMs; adjusted for the full set of potential confounders) were applied to explore the shape of the associations between each exposure biomarker and the log odds of the outcomes. Evidence of non-linearity was observed between maternal and infant fluoride concentrations with atopic eczema outcomes (P-gain < 0.1 and visual assessment; Supplemental Figures S3a and S4a). Thus, log$_2$-transformed fluoride concentrations, which were linearly associated with the logit of the allergy outcomes (Supplemental Figures S3b and S4b), were used in the analyses.

Logistic regression analyses were performed to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between exposures and outcomes. We estimated crude and adjusted ORs (in the minimally adjusted models for the a priori selected factors and in the fully adjusted models for all the potential confounders) for food allergy and atopic eczema, per one interquartile range (IQR) increase of the exposures. However, for maternal and infant urinary fluoride concentrations, which were log$_2$ transformed, the OR for each doubling in fluoride was estimated. The reference groups for food allergy and atopic eczema included individuals without food allergy and without atopic eczema, respectively.

In sensitivity analyses, the fully adjusted models of erythrocyte lead concentrations were additionally adjusted for maternal game meat intake at gestation (grams per day), and for any parent being a hunter. These factors may contribute to the exposure, since lead is used in ammunition, and they may also be reflective of a lifestyle previously associated with the outcomes under study, i.e., protective effect of farming lifestyle (regular contact with animals and pets) on allergic disease. The models of maternal erythrocyte mercury concentrations were additionally adjusted for fish intake biomarkers, i.e., erythrocyte n-3 LCPUFAs fractions and arsenic at gestational week 29, and the models of infant erythrocyte mercury concentrations for erythrocyte n-3 LCPUFAs fractions and arsenic at 4 months of age, as beneficial nutrients in fish have previously been shown to mask the detrimental effects of methylmercury in relation to other outcomes (Budtz-Jørgensen et al., 2007). Lastly, since previous studies have identified sex-related differences in allergic disease prevalence and sex-specific effects of various environmental exposures on child allergic disease (Kvalem et al., 2020; Margetaki et al., 2022), potential sex differences were assessed by inserting a multiplicative term between each exposure and infant sex in the models.

3. Results

3.1. Background characteristics and exposure data

The background characteristics of the 482 mother-infant pairs included herein are presented in Table 1. The mean maternal age at birth of the infants was 31 years (SD = 5), most of the mothers had a university degree (70%), the vast majority were non-smokers (94%), and almost half of the families had a pet at home (47%). Many families had an allergy history (parent or sibling; 69%). Eight percent of the infants

Table 1
Characteristics of the mother-infant pairs included in the study.

	N	Mean (±SD) or %
Maternal characteristics		
Age (years)	482	30.6 (4.7)
BMI in early pregnancy (kg/m^2)	482	25.5 (4.8)
Parity (%)	482	
Primiparous	235	49
Multiparous	247	51
Maternal education (university; %)	482	
No	146	30
Yes	336	70
Pre-pregnancy smoking status (%)	482	
No	452	94
Yes	30	6
Allergy history in the family (%)	482	
No	148	31
Yes	334	69
Pet ownership (%)	482	
No	256	53
Yes	226	47
Infant characteristics		
Gestational age at delivery (weeks)	482	40 (1.7)
Preterm delivery (< 37 GWs)	482	
No	464	96
Yes	18	4
Season of birth (%)	482	
Dark (October to March)	259	54
Bright (April to September)	223	46
Sex (%)	482	
Female	264	55
Male	218	45
Birth weight (grams)	481	3603 (551)
Breastfeeding between at 4 months (%)	462	
No	57	12
Yes	405	88
Food allergy diagnosis at 1 year	467	
No	428	92
Yes	39	8
Atopic eczema diagnosis at 1 year	482	
No	449	93
Yes	33	7

Abbreviations: SD: standard deviation; BMI: body mass index; GW, gestational week.

were diagnosed with food allergy at 1 year of age, 7% with atopic eczema and 2% with both. Table 2 summarizes maternal and infant exposure biomarker concentrations. Moderate positive correlations were observed between gestational and infant erythrocyte mercury (rho = 0.64; $P < 0.001$), gestational and infant erythrocyte lead (rho = 0.47; $P < 0.001$), gestational and infant urinary fluoride (rho = 0.31; $P < 0.001$).

Eighty-six percent of the infants were breastfed at 4th month postpartum. Exclusively breastfed infants had markedly lower urinary fluoride concentrations at 4 months of age (median [IQR] = 0.04 mg/L [0.03 mg/L]) than those who were exclusively formula fed (median [IQR] = 0.10 mg/L [0.14 mg/L]; $P < 0.001$). Conversely, exclusively breastfed infants had higher erythrocyte mercury concentrations (median [IQR] = 0.93 μg/kg [0.94 μg/kg]) than exclusively formula-fed infants (median [IQR] = 0.49 μg/kg [0.56 μg/kg]; $P < 0.001$). None of the other metal exposures differed between exclusively breast fed and formula feed infants (data not shown).

3.2. Associations of metal and fluoride exposure with food allergy or atopic eczema

Maternal urinary cadmium concentrations during pregnancy were associated with both increased odds of food allergy (OR [95% CI]: 1.34 [1.09, 1.66] per IQR [0.08 μg/L]) and atopic eczema (OR [95% CI]: 1.19 [0.96, 1.47] per IQR), although the latter was not statistically significant. Further adjustment for multiple potential confounders, including an allergy history in the family and child sex did not substantially change the estimates (Table 3). The mothers' urinary cadmium concentrations were moderately positively correlated with their gestational erythrocyte cadmium concentrations (rho = 0.43, $p < 0.001$), however, gestational erythrocyte cadmium was not associated either food allergy or atopic eczema (Table 3).

In contrast to cadmium, gestational erythrocyte lead concentrations were associated with decreased odds of atopic eczema (OR [95% CI]: 0.48 [0.26, 0.87] per IQR [6.57 μg/kg]). The estimates were not substantially changed after adjustment for potential confounders (Table 3). Similarly, infant erythrocyte lead concentrations at 4 months were associated with decreased odds of food allergy (OR [95% CI]: 0.39 [0.16, 0.93]; per IQR [5.94 μg/kg]) and atopic eczema (OR [95% CI]: 0.38 [0.16, 0.91]), although the latter association was weaker and not statistically significant in the fully-adjusted models (OR [95% CI]: 0.47 [0.18, 1.19]) (Table 4). In sensitivity analysis, further adjustment of the gestational lead models for game-meat intake during pregnancy or having a parent who is a hunter did not change the estimates (Supplemental Table S2).

Maternal urinary sum concentrations of metabolites of inorganic arsenic [inorganic arsenic, MMA, DMA]) were not associated with any of the outcomes (Table 3). In the initial analyses, neither gestational nor infant erythrocyte mercury concentrations were associated with the odds of allergic disease (Table 3 and Table 4). In the sensitivity analysis, further adjustment of the gestational mercury models for erythrocyte n-3 LCPUFA and arsenic (biomarkers of fish intake) increased the odds of atopic eczema (OR [95% CI]: 1.29 [0.80, 2.06]) and slightly increased the odds of food allergy (OR [95% CI]: 1.10 [0.70, 1.73]) (Supplemental Table S3), however, none of the associations became statistically significant. Further adjustment of the infant erythrocyte mercury models for infant erythrocyte n-3 LCPUFA and arsenic had marginal impact on all estimates (Supplemental Table S3).

Both gestational and infant urinary fluoride concentrations were

Table 2
Metal concentrations at gestational week 29 and at 4 months of age.

	N	Mean (±SD)	Median (IQR)	Range	5th-95th percentile
Maternal concentrations					
Erythrocyte cadmium (μg/kg)	482	0.36 (0.42)	0.29 (0.18)	0.05–5.69	0.13–0.71
Erythrocyte lead (μg/kg)	482	13.61 (10.69)	11.18 (5.75)	3.82–147.84	6.09–25.89
Erythrocyte mercury (μg/kg)	482	1.82 (1.30)	1.50 (1.42)	0.01–10.60	0.29–4.47
Urinary cadmium (μg/L)[a]	481	0.13 (0.10)	0.10 (0.08)	0.02–0.97	0.04–0.27
Urinary inorganic arsenic metabolites (μg/L)[a,b]	477	4.85 (5.19)	3.33 (3.49)	0.63–61.45	1.08–13.44
Urinary fluoride (mg/L)	467	0.86 (0.68)	0.71 (0.46)	0.07–6.4	0.33–1.9
Infant concentrations					
Erythrocyte lead (μg/kg)	210	10.64 (7.01)	8.51 (6.31)	1.02–44.5	4.03–21.79
Erythrocyte mercury (μg/kg)	210	1.02 (0.92)	0.83 (0.92)	0.01–6.62	0.05–2.37
Urinary fluoride (mg/L)[a]	321	0.07 (0.10)	0.04 (0.05)	0.01–0.93	0.02–0.25

Abbreviations: SD: standard deviation; IQR: interquartile range.
[a] Urinary cadmium, inorganic arsenic, and fluoride concentrations are adjusted for specific gravity.
[b] Inorganic arsenic metabolites: sum of inorganic arsenic (iAs), methylarsonic acid (MMA), and dimethylarsinic acid (DMA).

Table 3
Multivariable-adjusted logistic regression models of maternal metal concentrations in erythrocytes and urine at gestational week 29 in relation to food allergy and atopic eczema diagnosis at 1 year of age.

	Food Allergy			Atopic eczema		
	Controls	*Cases*	OR (95% CI)	*Controls*	*Cases*	OR (95% CI)
Gestational urinary cadmium (per IQR = 0.08 μg/L)[a]						
Crude	429	37	**1.34 (1.09, 1.66)**	449	32	1.19 (0.96, 1.47)
Minimally adjusted[b]	429	37	**1.36 (1.09, 1.69)**	449	32	1.17 (0.95, 1.45)
Fully adjusted[c]	429	37	**1.37 (1.09, 1.74)**	449	32	1.14 (0.91, 1.44)
Gestational erythrocyte cadmium (per IQR = 0.187 μg/kg)						
Crude	428	39	0.94 (0.74, 1.20)	449	33	0.97 (0.80, 1.19)
Minimally adjusted[b]	428	39	0.95 (0.73, 1.23)	449	33	0.99 (0.78, 1.24)
Fully adjusted[c]	428	39	0.95 (0.74, 1.22)	449	33	0.98 (0.76, 1.26)
Gestational erythrocyte lead (per IQR = 6.57 μg/kg)						
Crude	428	39	0.94 (0.73, 1.23)	449	33	**0.48 (0.26, 0.87)**
Minimally adjusted[b]	428	39	0.95 (0.73, 1.25)	449	33	**0.47 (0.25, 0.87)**
Fully adjusted[c]	428	39	0.95 (0.72, 1.25)	449	33	**0.50 (0.27, 0.91)**
Gestational erythrocyte mercury (per IQR = 1.36 μg/kg)						
Crude	428	39	0.93 (0.65, 1.34)	449	33	0.98 (0.67, 1.43)
Minimally adjusted[b]	428	39	0.95 (0.66, 1.36)	449	33	1.01 (0.70, 1.46)
Fully adjusted[c]	428	39	0.97 (0.66, 1.43)	449	33	1.02 (0.67, 1.55)
Gestational inorganic arsenic exposure (urinary sum of inorganic arsenic metabolites [iAs, MMA, DMA]; per IQR = 3.33 μg/L)[a]						
Crude	425	37	0.96 (0.75, 1.23)	445	32	0.94 (0.72, 1.24)
Minimally adjusted[b]	425	37	0.95 (0.74, 1.23)	445	32	0.94 (0.71, 1.25)
Fully adjusted[c]	425	37	0.97 (0.74, 1.25)	445	32	0.97 (0.72, 1.30)
Gestational urinary fluoride (log_2)[a]						
Crude	415	37	0.99 (0.65, 1.51)	435	32	1.48 (0.98, 2.25)
Minimally adjusted[b]	415	37	0.98 (0.65, 1.48)	435	32	1.44 (0.95, 2.17)
Fully adjusted[c]	415	37	0.95 (0.62, 1.45)	435	32	1.40 (0.91, 2.15)

Abbreviations: OR: odds ratio; CI: confidence interval; IQR: interquartile range; inorganic arsenic metabolites [sum of inorganic arsenic (iAs), methylarsonic acid (MMA), and dimethylarsinic acid (DMA)].

[a] Cadmium, arsenic, and fluoride urinary concentrations are adjusted for specific gravity; Fluoride concentrations are log_2-transformed.

[b] Minimally adjusted model is adjusted for allergy history in the family (parent or sibling; categorical; no or yes) and infant sex (categorical; male or female).

[c] Fully adjusted model is adjusted for allergy history in the family (parent or sibling; categorical; no or yes), infant sex (categorical; male or female), maternal age (continuous; years), maternal education (categorical; no university degree or university degree), maternal body mass index (BMI; continuous; kg/m^2), parity (categorical; primiparous or multiparous), maternal smoking (categorical; no or yes), pet ownership (categorical; no or yes), and season of birth [categorical; dark season (October to March) or bright season (April to September)].

associated with increased odds of atopic eczema (OR [95% CI]: 1.48 [0.98, 2.25] and OR [95% CI]: 1.36 [0.95, 1.95] per doubling of urinary fluoride), although the associations did not reach statistically significant levels. Adjustment for multiple potential confounders (Table 3 and Table 4), slightly weakened the association of gestational urinary fluoride and atopic eczema (OR [95% CI]: 1.40 [0.91, 2.15]), whereas the association of infant urinary fluoride and atopic eczema became stronger (OR [95% CI]: 1.43 [0.97, 2.12]).

Lastly, we did not find any significant multiplicative interaction between each exposure and infant sex for any of the studied associations (*P-value* > 0.05), indicating that the associations between exposure and allergic disease did not differ significantly by infant sex in our population.

Table 4
Multivariable-adjusted logistic regression models of infant metal concentrations in erythrocytes and urine at 4 months of age in relation to food allergy and atopic eczema at 1 year of age.

	Food Allergy			Atopic eczema		
	Controls	*Cases*	OR (95% CI)	*Controls*	*Cases*	OR (95% CI)
Infant erythrocyte lead (per IQR = 5.94 μg/kg)						
Crude	184	18	**0.39 (0.16, 0.93)**	192	18	**0.38 (0.16, 0.91)**
Minimally adjusted[a]	184	18	**0.36 (0.14, 0.92)**	192	18	**0.38 (0.15, 0.94)**
Fully adjusted[b]	184	18	**0.35 (0.13, 0.95)**	192	18	0.47 (0.18, 1.19)
Infant erythrocyte mercury (per IQR = 0.86 μg/kg)						
Crude	184	18	0.85 (0.49, 1.46)	192	18	0.74 (0.40, 1.38)
Minimally adjusted[a]	184	18	0.93 (0.53, 1.63)	192	18	0.81 (0.43, 1.51)
Fully adjusted[b]	184	18	0.94 (0.52, 1.70)	192	18	0.88 (0.43, 1.80)
Infant urinary fluoride (log_2)[c]						
Crude	287	23	1.11 (0.79, 1.56)	302	19	1.36 (0.95, 1.95)
Minimally adjusted[a]	287	23	1.12 (0.80, 1.57)	302	19	1.43 (0.98, 2.08)
Fully adjusted[b]	287	23	1.09 (0.77, 1.56)	302	19	1.43 (0.97, 2.12)

Abbreviations: OR: odds ratio; CI: confidence interval; IQR: interquartile range.

[a] Minimally adjusted model is adjusted for allergy history in the family (parent or sibling; categorical; no or yes) and infant sex (categorical; male or female).

[b] Fully adjusted model is adjusted for allergy history in the family (parent or sibling; categorical; no or yes), infant sex (categorical; male or female), maternal age (continuous; years), maternal education (categorical; no university degree or university degree), maternal body mass index (BMI; continuous; kg/m^2), parity (categorical; primiparous or multiparous), maternal smoking (categorical; no or yes), pet ownership (categorical; no or yes), and season of birth [categorical; dark season (October to March) or bright season (April to September)].

[c] Concentrations of fluoride in urine are adjusted for specific gravity and log_2-transformed.

4. Discussion

The present findings suggest that women's low-level exposure to cadmium during pregnancy may increase the odds of food allergy in their children at 1 year of age in the Swedish NICE cohort. We also found indications of a possible increase in the odds of atopic eczema in infancy in relation to prenatal and early-life exposure to fluoride. Unexpectedly, gestational exposure to lead appeared to be associated with decreased odds of atopic eczema and infant exposure to lead with decreased odds of both atopic eczema and food allergy. Although additional adjustment for fish intake biomarkers strengthened the association of gestational methylmercury exposure and infant atopic eczema, the confidence interval was still wide and the association non-significant. Also, there was no association between the low-level gestational exposure to inorganic arsenic and infant food allergy or atopic eczema disease.

We found maternal urinary cadmium concentrations, reflecting chronic exposure, to be associated with infant food allergy. To our knowledge, only a few previous studies have assessed the role of cadmium exposure in the development of allergic disease (Kim et al., 2019; Kim et al., 2013; Pesce et al., 2021). A French birth-cohort study (EDEN study; n = 651) reported that cord blood cadmium concentrations were positively associated with the risk of parent-reported atopic eczema, food allergy, and atopic asthma development by the age of 8 years (HR [95% CI]: 1.60 [1.09, 2.35], 3.17 [1.36, 7.38], 1.81 [1.00, 3.29], comparing the upper and lower exposure quartiles), while no association was identified between maternal erythrocyte cadmium concentrations during gestation and risk of allergic disease (Pesce et al., 2021). In a South Korean birth cohort (MOCEH study; n = 446), elevated cord blood cadmium concentrations were associated with increased odds of atopic dermatitis at 6 months (OR [95% CI]: 2.31 [1.13, 4.91]) (Kim et al., 2013). To note, the reported median cord whole blood cadmium concentration in the EDEN study was 0.5 μg/L (range 0.1–4.6 μg/L), compared to 0.8 μg/L in their mothers at late pregnancy, and in the MOCEH study the mean (SD) cord blood cadmium concentration was 0.71 ±0.28 μg/L with no data on maternal blood concentrations. These cord blood concentrations raise concern about exposure misclassification since cadmium has been shown to accumulate in the placenta with a limited amount passing to the fetus (usually < 10% of that in maternal blood) (Dong et al., 2023; Fagerstedt et al., 2015; Osman et al., 2000). In another South Korean birth-cohort (COCOA study; n = 331), with lower cord blood cadmium concentrations (median: 0.1 μg/L [range, 0–2.5 μg/L]), there was no significant association with atopic dermatitis up to 5 years of age (Kim et al., 2019). Like the EDEN study (Pesce et al., 2021), we did not find any association of maternal erythrocyte cadmium concentrations, reflecting short-term exposure, with food allergy or atopic eczema. Probably, blood concentrations measured in the third trimester may not accurately reflect cadmium exposure earlier in pregnancy, as cadmium absorption increases at poor iron stores, which is common during pregnancy, and also by pregnancy itself (Åkesson et al., 2002). Urinary concentrations, on the other hand, reflect chronic exposure since cadmium accumulates in the renal cortex with a half-life of decades (Akerstrom et al., 2013).

As cadmium does not readily cross the placenta (Fagerstedt et al., 2015; Osman et al., 2000), a direct effect of gestational cadmium exposure on fetal immune development seems unlikely. Instead, it has been speculated that the placental accumulation may indirectly impact the development of the immune system through impaired transfer of nutrients, e.g., zinc to the fetus (Holásková et al., 2012; Kippler et al., 2010), but mechanistic evidence is not available. The association may also be mediated by alterations of fetal programming caused by cadmium-induced changes in DNA methylation very early in gestation (Kippler et al., 2013). On the other hand, we cannot exclude the possibility that long-term maternal cadmium exposure is a proxy of unmeasured lifestyle factors that are linked to the development of allergic disease (hygiene hypothesis) (Strachan, 1989), as cadmium originates mainly from healthy foods such as cereals and vegetables (Gustin et al., 2020), although the observed association with food allergy was unaffected by adjustment for multiple lifestyle-related factors.

Unexpectedly, early-life exposure to lead, measured by concentrations in maternal erythrocytes during gestation and in infant erythrocytes at 4 months of age, appeared to be associated with decreased odds of food allergy and atopic eczema. The few previous studies on the immune system effects of early life lead exposure are inconclusive (WHO, 2012). However, several studies in adults as well as experimental models suggest that lead exposure can induce immune function alterations that predict atopic diseases (Dietert & Piepenbrink, 2006; Wang et al., 2022; WHO, 2012). Lead exposure in the NICE mothers was found to be correlated with intake of game meat, such as moose and hare (Gustin et al., 2020), and such consumption was more common in the countryside than in more urban areas (Stråvik et al., 2019). Thus, it is possible that such a lifestyle shares several characteristics of a farming lifestyle, which has previously been found to be protective against child allergy (Jonsson et al., 2016a), although few of the participating families lived on a farm (Stråvik et al., 2019). However, additional adjustment for game meat intake during gestation or hunting (any of the parents) did not affect the inverse associations of erythrocyte lead with the odds of infant allergy. Also, consumption of milk, which was protective against allergy in the NICE children (Stråvik et al., 2020) and was, like game meat, more often consumed in the countryside (Stråvik et al., 2019), is known to inhibit the gastrointestinal absorption of lead, resulting in lower blood lead levels (Kordas et al., 2018). Obviously, further cohort studies are warranted to elucidate whether the unexpected lead-allergy associations reflect a role of lead in the development of allergic disease or if they were observed merely due to unmeasured residual confounding.

Methylmercury is a highly toxic environmental pollutant which is actively transported across the placenta (Kajiwara et al., 1996). In the present study, methylmercury exposure was not associated with infant atopic eczema or food allergy in the main analyses. In sensitivity analyses, a positive association was observed between maternal methylmercury exposure and atopic eczema odds after additional adjustment for biomarkers of fish intake, but it was still statistically non-significant. Intake of contaminated fish is usually the sole source of methylmercury exposure (World Health Organization, 2008). Indeed, maternal erythrocyte mercury concentrations, reflecting methylmercury exposure, showed the strongest correlation with the intake of both fatty and lean fish among a range of potential biomarkers of seafood intake in the NICE women (Stråvik et al., 2023). Also, fish intake has been suggested to prevent development of allergic disease (Jonsson et al., 2016b; Miles and Calder, 2017) and protect against atopic eczema in children (Hesselmar et al., 2010; Romieu et al., 2007; Sausenthaler et al., 2007). Our finding emphasizes that appropriate adjustment for fish intake is essential when exploring relationships of contaminants or nutrients in fish with health outcomes to control for the contradictory effects.

To our knowledge this is the first study to suggest a potential positive association between early-life fluoride exposure and having a diagnosis of infant atopic eczema. There was a wide variation in maternal urinary fluoride (total range of urinary fluoride 0.07–6.4 mg/L, specific gravity adjusted), which probably derived from drinking water, tea intake, and dental care products (National Research Council, 2007). Fluoride readily crosses the placenta (Malhotra et al., 1993), but little is excreted in breast milk (National Research Council, 2007). So, because of the high prevalence of breastfeeding in the present study (almost 90%), the infant urinary fluoride concentrations were quite low (5^{th}-95^{th} percentile: 0.02–0.25 mg/L). Still, the odds of eczema with infant exposure were similar to those with the mothers' exposure, with an almost 20 times higher median urinary fluoride concentration. Although there are no previous cohort studies to compare the present results with, *in vitro* studies using rodent immune cells have suggested that fluoride exposure is linked to several immune function alterations implicated in allergic diseases (e.g., in macrophage population, in inflammatory biomarkers concentrations, in expression levels of surface proteins in B cells) (De la

Fuente et al., 2016; Ma et al., 2016; Ma et al., 2017; Shi et al., 2016). There is emerging epidemiological evidence of a link between early-life fluoride exposure and adverse neurodevelopmental effects (Grandjean, 2019) and with large birth size (Kampouri et al., 2022), which highlights the need for investigation of possible further developmental effects of early-life fluoride exposure.

The main strengths of the present study include the prospective design and that the diagnosis of allergy was performed by a paediatrician specialized in allergy. Also, we used appropriate exposure biomarkers to assess gestational and early-life exposure to toxic metals and fluoride. The exposure levels were relatively low, but only a few samples had concentrations below the LOD, except for cadmium in infant erythrocytes, for which 60% of the samples had concentrations below the detection limit (0.07 μg/kg). Therefore, we decided not to perform analyses to assess the association of infant cadmium concentrations with allergic disease. Both fluoride and inorganic arsenic metabolites concentrations in urine reflect contemporary exposure, which may have limited the statistical power to detect associations between these exposures and allergic disease. Also, the limited number of cases in this study (which was the result of a relatively small sample size and the assessment of allergic disease very early in life), combined with the inclusion of multiple potential confounders in logistic regression models, may have resulted in overfitting in the fully adjusted models. Nevertheless, the estimates remained stable between the crude and the adjusted models, indicating that potential overfitting did not significantly impact the fully adjusted models. We cannot exclude the possibility that unmeasured residual confounding has affected the reported findings, although the analyses were not changed after adjustment for multiple potential confounders and the associations appeared robust. Lastly, the pregnant women in the NICE cohort differ in background characteristics such as age, educational level, and lifestyle (i.e., cohabitation with partner, smoking status, and supplement use during pregnancy) compared to other non-participating pregnant women within Norrbotten County in northern Sweden (Ögge et al., 2022). Although, these differences did not alter pregnancy outcomes known to be related with lifestyle parameters, we cannot exclude that they may have affected the generalizability of the reported findings.

In conclusion, the present results suggest, that even low-level maternal exposure to cadmium, measured in gestation, is associated with increased odds of food allergy in their children at one year of age. Also, the results indicate that exposure to fluoride may be associated with increased odds of atopic eczema. Conversely, low-level lead exposure, measured in mothers during gestation and in infants at 4 months, was associated with decreased odds of atopic eczema and food allergy at one year. The observed associations did not change after adjustment for multiple lifestyle factors. Nevertheless, further prospective studies with detailed information on lifestyle factors and experimental mechanistic studies are needed to elucidate causality, as we cannot exclude the impact of residual confounding in any of the present findings.

CRediT authorship contribution statement

Mariza Kampouri: Visualization, Investigation, Writing – original draft, Writing – review & editing. **Klara Gustin:** Writing – review & editing. **Mia Stråvik:** Writing – review & editing. **Malin Barman:** Writing – review & editing. **Anna Sandin:** Project administration, Writing – review & editing. **Ann-Sofie Sandberg:** Project administration, Writing – review & editing, Funding acquisition. **Agnes E. Wold:** Funding acquisition, Project administration, Writing – review & editing. **Marie Vahter:** Conceptualization, Project administration, Supervision, Investigation, Methodology, Funding acquisition, Writing – review & editing. **Maria Kippler:** Conceptualization, Supervision, Investigation, Methodology, Funding acquisition, Project administration, Writing – review & editing.

Declaration of Competing Interest

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

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary material

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