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Low-level maternal exposure to cadmium, lead, and mercury and birth outcomes in a Swedish prospective birth-cohort☆

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ABSTRACT

Observational studies have indicated that low-to-moderate exposure to cadmium (Cd), lead (Pb), and mercury (Hg) adversely affects birth anthropometry, but results are inconclusive. The aim of this study was to elucidate potential impact on birth anthropometry of exposure to Cd, Pb, and Hg in pregnant women, and to identify the main dietary sources. In the NICE (Nutritional impact on Immunological maturation during Childhood in relation to the Environment) birth-cohort in northern Sweden, blood and urine were collected from pregnant women in early third trimester. Cd, Pb and Hg were measured in erythrocytes (n = 584), and Cd also in urine (n = 581), by inductively coupled plasma mass spectrometry. Dietary data were collected through a semi-quantitative food frequency questionnaire administered in mid-third trimester. Birth anthropometry data were extracted from hospital records. In multivariable-adjusted spline regression models, a doubling of maternal erythrocyte Cd (median: 0.29 μg/kg) above the spline knot of 0.50 μg/kg was associated with reduced birth weight (B: −191 g; 95% CI: −315, −68) and length (−0.67 cm; −1.2, −0.14). The association with birth weight remained when the analysis was restricted to never-smokers. Likewise, a doubling of erythrocyte Hg (median 1.5 μg/kg, mainly MeHg) above 1.0 μg/kg, was associated with decreased birth weight (−59 g; −115, −3.0), and length (−0.29 cm; −0.54, −0.047). Maternal Pb (median 11 μg/kg) was unrelated to birth weight and length. Erythrocyte Cd was primarily associated with intake of plant derived foods, Pb with game meat, tea and coffee, and Hg with fish. The results indicated that low-level maternal Cd and Hg exposure were associated with poorer birth anthropometry. Further prospective studies in low-level exposed populations are warranted.

1. Introduction

The toxic metals cadmium (Cd), lead (Pb), and mercury (Hg), are all found among the top 10 chemicals of major public health concern according to the World Health Organization (WHO, 2007, 2010, 2019), and they are all ubiquitous in the environment. In the general non-smoking population, exposure to Cd, Pb, and Hg occurs mainly via consumption of contaminated food (EFSA, 2010, 2012a, 2012b), Hg mainly in the organic form of methylmercury (MeHg). However, the type of dietary sources of exposure to these metals may vary considerably between countries and food habits (EFSA, 2010, 2012a, 2012b). During pregnancy, maternal blood Cd

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accumulates in the placenta, potentially causing placental toxicity (Kippler et al., 2010; Punshon et al., 2019), Pb passes across the placenta to the fetus (Agrawal, 2012), and MeHg is transported actively to the fetus (Bjornberg et al., 2005). Both Pb and MeHg are well-known developmental neurotoxicants (EFSA, 2010, 2012b), and more recently, maternal Cd exposure has also been found to be inversely associated with neurodevelopment (Gustin et al., 2018; Liu et al., 2019).

Birth weight is a significant predictor of perinatal morbidity (Katz et al., 2013), as well as health later in life (Gluckman et al., 2008; Murai-Takeda et al., 2019). In a recent meta-analysis (Khoshhali et al., 2019), including 19 studies, low-to-moderate maternal Cd exposure in pregnancy was considered inversely associated with birth weight, but not with birth length or head circumference. Studies of the impact of low-level maternal Pb exposure during pregnancy on birth anthropometry have so far been inconclusive (Allen, 2015; Rodosthenous et al., 2017; Tatsuta et al., 2017; Wang et al., 2017). Likewise, associations of low-level maternal Hg exposure with birth anthropometry, although much less studied than Cd and Pb, have varied (Karagas et al., 2012). In a recent Spanish study, total Hg concentrations in cord blood were inversely associated with fetal biparietal diameter, but not with femur length, abdominal circumference or estimated fetal weight (Ballester et al., 2018).

Taken together, there are indications that maternal exposure to Cd, Pb, and Hg may adversely affect infant anthropometry, yet the results are still conflicting concerning the low-to-moderate exposure levels commonly occurring in food. Thus, the aim of the present study was to elucidate the potential impact on birth anthropometry of exposure to Cd, Pb, and Hg in pregnant women in a Swedish birth-cohort, and to identify the main dietary sources.

2. Methods

2.1. Study population

The present study is based on an ongoing prospective birth-cohort in northern Sweden (Nutritional Impact on the Immunological Maturation during Childhood in relation to the Environment; NICE). The primary aim of the NICE study is to assess the influence of the diet and other key environmental factors in early-life on the immune maturation and allergy development in children. Secondary outcomes include infant and child anthropometry and neurological development (Barman et al., 2018). The cohort was established in the catchment area of Sunderby hospital in Norrbotten county, Sweden. All expectant parents planning to give birth at Sunderby Hospital during 2015–2018 received an information leaflet at their visit to the local maternity clinics. At the routine ultrasound in gestational week 17–18, parents who were interested in participation were given more information and an informed consent to sign at home and send back. To be included in the study, families had to be residents in Norrbotten county and be able to communicate in written and spoken Swedish.

In all, 655 pregnancies were included in the NICE study (Fig. 1), 18 of which were second pregnancies in already participating families. In this study, only data from the first pregnancy was included, except for two families where the first child was stillborn (in gestational week 29 and 37, respectively), for which data from the second pregnancy was included. We excluded additional stillbirths ($n = 2$; in gestational week 35 and 37, respectively), miscarriages ($n = 1$; in gestational week 18), twin births ($n = 3$), and one family that withdrew from the study, resulting in a total of 630 eligible mother-child dyads. Of these, 589 had donated maternal blood ($n = 584$) and/or urine ($n = 581$) in pregnancy and had complete data on birth weight. The multivariable-adjusted models for birth weight with blood and urine biomarkers included 558 and 555 mother-child dyads, respectively, due to missing information on maternal education ($n = 7$), early-pregnancy BMI ($n = 16$), pre-pregnancy smoking ($n = 3$), and gestational age ($n = 1$). For birth length and head circumference the corresponding numbers were 545 and 542, respectively, due to missing birth anthropometry data.

The study was approved by the Regional Ethical Review Board, Umeå, Sweden, (2013/18-31M, 2018-256-32M), and performed in accordance with the Helsinki declaration. At enrollment, the parents provided a written consent about their own participation and at the time of delivery they provided an additional written consent about the participation of their child. The participants were informed that they were free to withdraw from the study at any given time without further explanation.

2.2. Sample collection

Venous blood and spot urine samples were collected from the mothers at the local maternity health clinics around gestational week 28 (mean: 29; range: 24–36). Blood samples were collected in 6 mL trace element-free Na-heparin tubes (Greiner bio-one, Kremsmünster, Austria). Mid-stream spot urine samples were collected in urine collection cups and then transferred to 24-mL polyethylene bottles, both containers tested free of trace elements. All samples were stored at the local clinics at 4 °C until transported cold to the hospital laboratory the same or following workday. At the hospital laboratory, blood samples were centrifuged at 2400 rpm for 5 min at 4 °C (Hettich Rotina 420, Hettich Lab Technology, Tuttlingen, Germany), and the erythrocyte and plasma fractions were separated and aliquoted on a cooling block. All samples were stored at −20 to −80 °C before being transported frozen to Karolinska Institutet, Sweden, for trace element analysis.

2.3. Trace element analyses

Metal exposure in pregnancy was assessed by concentrations of Cd, Pb, and total Hg in maternal erythrocytes, reflecting exposure over the past 1–3 months (Carlson and Friberg, 1957; Schultze et al., 2014; Clarkson and Magos, 2006). For Cd we also measured the concentration in urine, as this is a widely used biomarker of chronic Cd exposure, due to the accumulation of Cd in the kidneys with a half-life of 10–45 years (Akerstrom et al., 2013; Amzal et al., 2009).

The metal concentrations in erythrocytes and urine were measured using inductively coupled plasma mass spectrometry (ICP-MS; Agilent 7700x, Agilent Technologies, Tokyo, Japan), equipped with an octopole reaction system. Cadmium (isotope 111) was measured in helium mode, whereas both Pb (isotope 208) and Hg (isotope 202) were measured in no gas mode. Prior to the ICP-MS analyses, erythrocyte samples were diluted 1:25 in an alkali solution [2% (w/v)1-butanol, 0.05% (w/v) EDTA, 0.05% (w/v) Triton X-100, 1% (w/v) NH_4OH and 20 μg/L internal standard] and vortex mixed, then sonicated for 5 min and centrifuged at 1000 rpm for 2 min (MSE centrifuge, Super Minor, MSE (UK) Ltd, London, England) (Lu et al., 2015). The limit of detection (LOD; calculated as 3 times the standard deviation of the blank concentration) was 0.0037 μg/kg, 0.11 μg/kg, and 0.010 μg/kg for Cd, Pb, and Hg, respectively. No sample had a concentration below the LOD for either Cd or Pb, but two samples had a concentration below the LOD for Hg, which were replaced by LOD/$\sqrt{2}$. Quality control of the ICP-MS analyses of erythrocyte metals was performed by inclusion of two commercial reference materials of whole blood and obtained values were in good agreement with the reference values (Table S1). Urine samples were diluted 1:10 in 1% nitric acid (67–69% w/w, NORMATOM®, VWR, Butterworth, UK). The LOD was

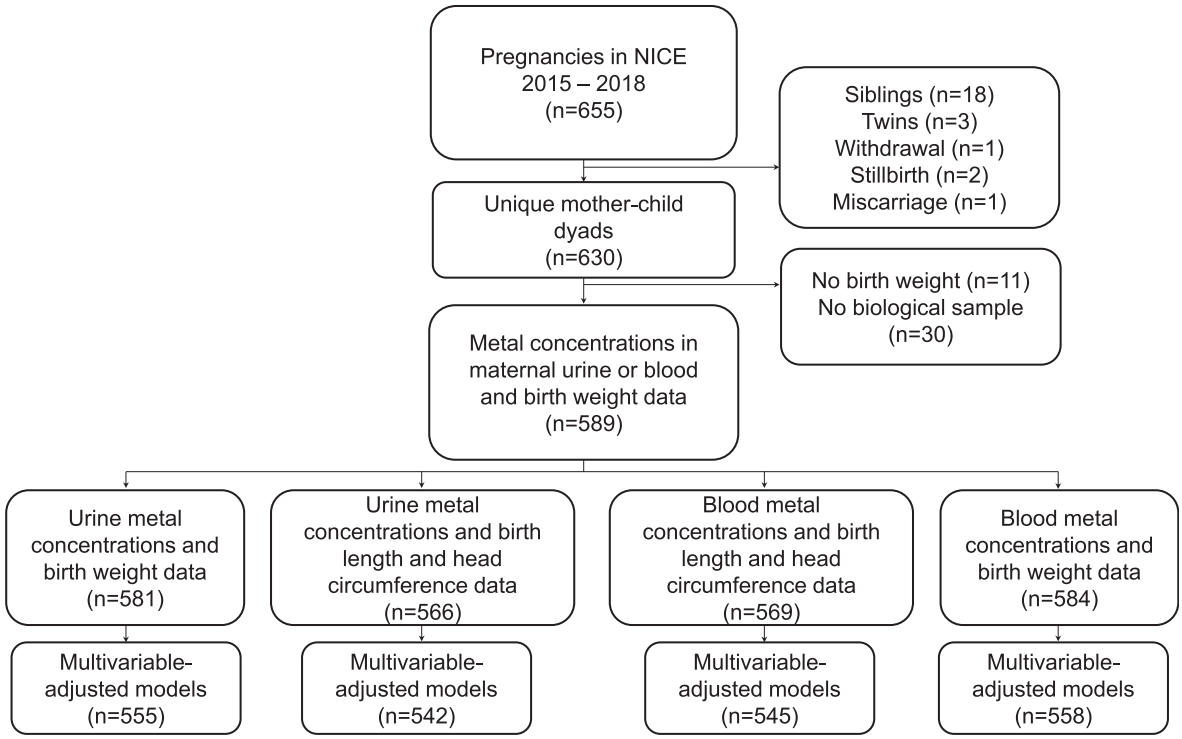

Fig. 1. Flowchart of the mothers and children included in the present study.

0.003 μg/L and no urine sample had a Cd concentration below this limit. We included two commercial reference materials of urine in each run, and in general the obtained values were in good concordance with the reference values (Table S1). To compensate the urinary concentrations for the variation in urine dilution, the specific gravity of each urine sample (SG_{sample}) was measured with a refractometer (ATAGO 4454 PAL-54S Digital Hand-Held Pocket Clinical Inspection Refractometer, Japan), and all urinary concentrations (C) were then adjusted (C_{adj}) to the mean specific gravity (SG_{mean}) of 1.017, using the following formula: $C_{adj} = C \times (SG_{mean}-1)/(SG_{sample}-1)$, as reported previously (Nermell et al., 2008).

2.4. Birth anthropometry

Information on the infants' weight (g), length (cm), and head circumference (cm) at birth was collected from the hospital records at Sunderby hospital. Due to the lack of consensus on standard growth curves, classification of weight derived small-for-gestational age was based on three different Northern European standard growth curves; ultrasound-based growth curves (Marsal et al., 1996) defined as below −2 SD from the mean, population-based growth curves (Skjaerven et al., 2000) defined as below the 10th percentile, and customized growth curves (adjusted for maternal weight, height, and parity; Gardosi et al., 1992) defined as below the 10th percentile. The standard deviations and percentiles used were those of the reference populations, and not the present study population.

2.5. Dietary data

Information regarding the mothers' diet during pregnancy was collected using a semi-quantitative food frequency questionnaire (FFQ), an adapted version of the validated Meal-Q questionnaire (Christensen et al., 2013; Christensen et al., 2014), as previously described (Stravik et al., 2019). In short, the FFQ was sent to the pregnant women by e-mail around gestational week 34 and included 102–174 questions (depending on follow-up questions) regarding intake frequency (times per day or week) of food items, and the consumed volume, over the past month. Accompanying pictures showed portion sizes of carbohydrates (pasta, rice and potato), protein (meat, fish and vegetarian alternatives) and vegetables. Based on reported portion size and intake frequency, the intake in gram per day was estimated. For other food items, normal portions according to the Swedish national food database managed by the Swedish Food Agency (SFA, 2020) was used. Intake of beverages was registered as the intake frequency of a predefined volume. After quantifying the dietary intake, intake of food items in gram per day were grouped to create "total intake" of a certain food, for instance fish. In addition, a proxy for a lacto-ovo vegetarian diet was constructed for mothers who reported a consumption of all meat and fish food items less than once a month (the lowest frequency possible to report). A list of all included food groups and their content is presented in Table S2.

2.6. Covariates

Information on maternal age (years), early-pregnancy body mass index (BMI; calculated based on body weight and height recorded at registration at the maternity clinic in the first trimester), parity (number of previous births), education (elementary school, high school, or university), pre-pregnancy smoking (never, sometimes, or daily), pre-pregnancy snuff or non-smoking tobacco use (never, sometimes, or daily), pre-pregnancy alcohol consumption (never, sometimes, or daily), and marital/cohabitant status (married, cohabitant, or other) was obtained from the hospital records. We used pre-pregnancy data regarding the mothers' tobacco use and alcohol consumption as information on maternal smoking and alcohol consumption in the third trimester was available only for a sub-set of the included mothers (n = 447 and n = 385, respectively), out of whom few or

none reported to be smoking or drinking in late pregnancy (n = 6 and n = 0, respectively).

Information on infant sex and gestational age at birth (in days), was obtained from hospital records. Pre-term birth was defined as delivery prior to gestational week 37.

2.7. Statistical analyses

Statistical analyses were performed using the software Stata/IC 15.0 (StataCorp, TX, USA) and R 3.6.2 (R Core Team, 2019). P-values below 0.05 were considered significant for all tests, but we also considered consistency and robustness of the results.

Associations between metal concentrations (maternal erythrocyte concentrations of Cd, Pb and Hg, and urinary Cd) and food intake data were explored among the never-smoking mothers (n = 549) with Spearman rank test, and further investigated with unsupervised hierarchical cluster analysis, visualized in a heat map using the R package *pheatmap* (Kolde, 2019). In the heat map, the data was automatically structured based on the correlation between variables, forming clusters by placing correlated variables close to each other. The magnitude of the correlation was indicated by color, where red indicated positive correlations and blue indicated negative correlations. Additional associations between maternal Cd concentrations and consumption of a lacto-ovo vegetarian diet (y/n) and of soy-based foods (y/n), and between erythrocyte Hg and maternal consumption of freshwater fish (y/n), were explored with Mann-Whitney *U* test.

Bivariate associations between the maternal metal concentrations and birth outcomes (birth weight, length, head circumference, and being born small-for-gestational age), and with potential covariates, were initially explored with either Spearman rank test (continuous variables), Mann-Whitney *U* test or Kruskal-Wallis test (continuous and categorical variables), or chi-square test (categorical variables).

All the measured metal concentrations were then $\log_2$-transformed (due to right-skewedness), and linearity of the $\log_2$-transformed concentrations with children's birth anthropometry was checked with scatter plots with moving average Lowess curves. These indicated a tendency of non-linear (inverted U-shape) relationships for erythrocyte Cd and Hg with birth weight (Figs. S1A and B) and birth length (Figs. S2A and B), and for erythrocyte Pb and Hg with head circumference (Figs. S3A and B). Therefore, these associations were explored with linear spline regression models. The position of the spline knot for each association was visually determined from the moving average Lowess curves (Figs. S1–S3). Several positions of the spline knots were explored for each association and the position that gave the highest adjusted R^2 was used.

Since the moving average Lowess curves indicated linear relationships between erythrocyte Cd and head circumference, and for erythrocyte Pb with birth weight and birth length, as well as for urinary Cd and all three measures of anthropometry, these associations were further explored with linear regression analyses.

The associations in the spline regression models and the linear regression models were explored adjusting for several covariates that were either selected *a priori* (infant sex and gestational age at birth) or that were associated ($p < 0.05$) with both the exposure biomarkers and the outcomes [early-pregnancy BMI, parity, maternal education (categorized into two groups: 'lower than university', and 'university'), and maternal pre-pregnancy smoking (categorized into two groups: 'never', and 'sometimes or daily')]. We additionally performed sub-group analyses by exploring the associations between maternal metal concentrations and birth anthropometry only in mothers who were never-smokers. As MeHg exposure comes almost exclusively from fish consumption, and fish intake may affect child growth (Stratakis et al., 2016), the associations of maternal erythrocyte Hg with birth anthropometry were also explored with additional adjustment for the mothers' total intake of fish (g/day). Since previous studies have indicated that the toxicity of Cd, Pb, and Hg might be modified by infant sex (Kippler et al., 2012; Tatsuta et al., 2017; Wang et al., 2017), we included multiplicative interaction terms between the metal concentrations and infant sex in all the regression models. Further, we also explored mutually adjusted standardized estimates (β) for each of the erythrocyte exposure biomarkers in relation to the anthropometric measurements by including all exposure biomarkers in the same model and adding the *beta* option for linear regression in Stata, which standardizes all variables to have a mean of 0 and a standard deviation of 1. Potential multicollinearity of the mutually adjusted models was checked with variance inflation factors (VIFs). Lastly, associations of potential joint effects of mixed exposure to Cd, Pb, and Hg on birth anthropometry were explored with Bayesian kernel machine regression (BKMR; Bobb et al., 2015). We conducted the BKMR with centered and scaled metal concentrations (the concentration subtracted by the mean divided by the standard deviation), applying the option of variable selection and 25 000 iterations by the Markov chain Monte Carlo algorithm. Due to the BKMR being sensitive to outliers, extreme erythrocyte concentrations of Cd (>2.7 μg/kg; n = 4) and Pb (>77 μg/kg; n = 4) were omitted from the analyses (total number of omitted observations: n = 8). All BKMR analyses were adjusted for the same covariates as the linear regression models. The BKMR analyses were performed using the R package *bkmr* (Bobb, 2017).

Associations between maternal metal concentrations and the child being born small-for-gestational age were explored with multivariable-adjusted logistic regression models, adjusted as the regression models above except for infant sex and gestational age at birth (incorporated in the outcomes), and performed separately for all and never-smoking mothers. To identify potential non-linear relationships, the exposure biomarkers were categorized into tertiles for all the logistic regression models. We used p for trend values to explore potential trends in the dose-response relationships. The p for trend values were obtained by creating a variable for each biomarker where the individual concentration of each sample was replaced by the median concentration of its tertile. The created variables were then included in their respective models as continuous variables.

3. Results

3.1. Background characteristics

General characteristics of the 589 included mothers and infants are presented in Table 1. The mean age of the mothers was 31 years (range: 19–45), and their mean early-pregnancy BMI was 25 kg/m^2 (range: 17–50). Forty-nine percent of the women were nulliparous. Most of the mothers had a university education (70%), and only 6.3% of them were smoking (sometimes or daily) prior to pregnancy. We had incomplete data on maternal smoking in late pregnancy but among the mothers for whom we had the information (n = 477), only six reported smoking sometimes or daily in pregnancy. Among the newborns, 53% were girls and the mean gestational age at birth was 40^{+0} weeks (range: 30^{+4}-42^{+5}), with a total of 4.3% (n = 25) pre-term births. The mean birth weight for girls was 3522 (SD: 516) g and for boys 3678 (SD: 589) g, mean birth length was 50 (SD: 2.1) and 51 cm (SD: 2.4) for girls and boys, respectively, and mean head circumference was 35 (SD: 1.4) and 35 cm (SD: 1.6), respectively. Birth weight correlated positively with birth length (r_s: 0.80; $p < 0.001$) and head circumference (r_s: 0.66; $p < 0.001$), as did birth length with head circumference (r_s: 0.57; $p < 0.001$). The prevalence of being born small-for-gestational

Table 1
Characteristics of the included mothers and infants.

Characteristics	n	Mean (SD), or %	Median (range)	5th-95th percentile
Mothers				
Age (y)	589	31 (4.7)	30 (19–45)	23–39
Early-pregnancy weight (kg)	572	71 (14)	68 (43–137)	53–100
Height (cm)	589	167 (6.0)	167 (149–184)	158–178
Early-pregnancy BMI	573	25 (4.9)	24 (17–50)	19–35
Number of previous pregnancies	589	0.73 (0.88)	1 (0–6)	0–2
Nulliparity (% yes)	289	49		
Education (% elementary/high school/university)	582	2/28/70		
Pre-pregnancy smoking (% yes)	586	6.3		
Erythrocyte Cd (μg/kg)	584	0.37 (0.42)	0.29 (0.05–5.7)	0.14–0.77
Urinary Cd (μg/L)[a]	581	0.13 (0.10)	0.10 (0.02–1.1)	0.04–0.27
Erythrocyte Pb (μg/kg)	584	14 (11)	11 (3.2–148)	6.0–27
Erythrocyte Hg (μg/kg)	584	1.8 (1.3)	1.5 (<0.01–11)	0.29–4.4
Infants				
Sex (% girls)	589	53		
Gestational age (weeks)	588	40 (1.7)	40 (31–43)	37–42
<37 weeks (% yes)	25	4.3		
Birth weight (g)	589	3595 (556)	3570 (1770–5165)	2730–4510
Ultrasound based SGA (<mean −2 SD; % yes)	588	1.5		
Population based SGA (<10th percentile; % yes)	589	9.3		
Customized SGA (<10th percentile; % yes)	562	16		
Birth length (cm)	574	50 (2.3)	50 (41–58)	47–54
Birth head circumference (cm)	575	35 (1.6)	35 (29–39)	32–38

Abbreviations: BMI, body mass index; Cd, cadmium; Hg, mercury; Pb, lead; SD, standard deviation; SGA, small for gestational age.
[a] Concentrations adjusted to the mean specific gravity of 1.017.

age was 1.5% (n = 9) according to ultrasound-based growth curves and definition (below mean −2 SD; Marsal et al., 1996), 9.3% (n = 55) according to the population based growth curves (Skjaerven et al., 2000) and 16% (n = 92) according the customized growth curve (Gardosi et al., 1992) and their definition (10th percentile).

The median concentration of Cd, Pb, and Hg in erythrocytes was 0.29 μg/kg (range: 0.05–5.7), 11 μg/kg (range: 3.2–148), and 1.5 μg/kg (range: <0.01–11), respectively. There were no strong correlations between the studied metals (Table S3). Erythrocyte Cd and Pb were very weakly positively correlated (r_s: 0.16; $p < 0.001$), as were erythrocyte Pb and Hg (r_s: 0.13; $p = 0.001$), but not erythrocyte Cd and Hg (r_s: −0.03; $p = 0.49$). Erythrocyte Cd was higher among pre-pregnancy smokers (n = 37) than among never-smokers (median: 0.55 *vs* 0.28 μg/kg, $p < 0.001$). The median maternal concentration of urinary Cd was 0.10 (range: 0.02–1.1) μg/L. The urinary Cd concentrations correlated positively with erythrocyte Cd (r_s: 0.43; $p < 0.001$) and maternal age (r_s: 0.32; $p < 0.001$), and were also marginally higher among pre-pregnancy smokers (median: 0.12 μg/L) than never-smokers (median: 0.10 μg/L; $p = 0.006$).

3.2. Maternal diet and metal exposure biomarkers

The unsupervised clustering analyses indicated very different associations with consumed food groups for the three metals (Fig. 2). As shown in Fig. 2 and Table S4, the mothers' erythrocyte Cd was significantly positively associated with their intake of root vegetables, vegetables, whole grain, rice, and nuts and seeds, and inversely associated with red meat consumption. Similarly, urinary Cd was positively associated with consumption of root vegetables and vegetables and inversely associated with red meat consumption and consumption of dairy products. Erythrocyte Pb was positively associated with game meat, as well as tea, coffee, and shellfish. Maternal erythrocyte Hg concentrations showed the strongest association with total fish intake, followed by shellfish intake, but was also positively associated with intake of root vegetables, vegetables, eggs, nuts and seeds, tea, coffee, and meat, and inversely associated with intake of chocolate and refined grains.

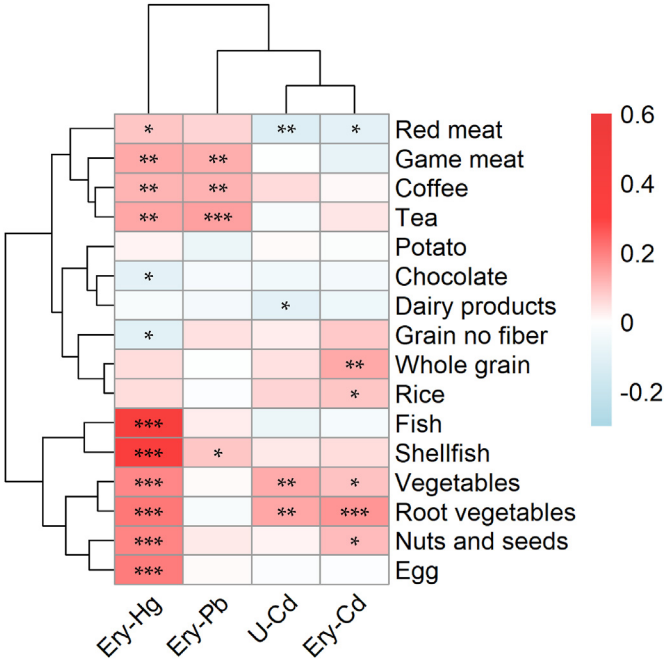

Fig. 2. Clustered heat map of bivariate correlations between the never-smoking mothers' consumption of different food groups and their concentration of cadmium in erythrocytes (Ery-Cd) and urine (U–Cd) and concentrations of lead (Ery-Pb) and mercury (Ery-Hg) in erythrocytes. The associations are based on the Spearman rank correlation test and the direction and magnitude of the correlation is denoted by color, with red representing positive associations and blue representing negative associations, and deeper colors signifying stronger correlation. Asterisks denote statistical significance: *p < 0.05, **p < 0.01, ***p < 0.001. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

We additionally found that erythrocyte Cd was markedly higher among mothers with a lacto-ovo vegetarian diet (median: 0.50 μg/kg; range: 0.24–0.65 μg/kg) than among those who consumed a

mixed diet that comprised meat and fish (median: 0.29 μg/kg; range: 0.054–5.7 μg/kg; p = 0.022). The few mothers reporting any intake of soy-based foods (n = 14) had higher erythrocyte Cd concentrations than those who reported no consumption (median: 0.38 and 0.29 μg/kg, respectively; p = 0.012). Only three of the mothers who reported intake of soy-based products were classified as being lacto-ovo vegetarians. Also, we explored maternal Hg concentrations with consumption of specific types of fish and found that erythrocyte Hg was correlated with consumption of both fatty fish (r_s: 0.41; p < 0.001), lean fish (r_s: 0.28; p < 0.001), and tuna (r_s: 0.27; p < 0.001), but not with freshwater fish consumption. However, very few of the mothers consumed freshwater fish during pregnancy (2.7%), while consumption of fatty fish in pregnancy was common (84%).

3.3. Metal concentrations in pregnancy and infant birth anthropometry

In bivariate analyses, maternal metal concentrations in pregnancy were not significantly associated with any of the infant birth anthropometry measures (Table S3). In the multivariable-adjusted spline regression model (Table 2), a doubling of maternal erythrocyte Cd above 0.50 μg/kg (log_2-transformed) was associated with a mean decrease in birth weight by −191 g (95% CI: −315, −68) and a mean decrease in birth length by −0.67 cm (95% CI: −1.2, −0.14). We found no association between erythrocyte Cd and head circumference. In sub-group analysis, including only never-smokers (Table 2), the inverse association of maternal erythrocyte Cd above 0.50 μg/kg with birth weight remained (B: −313; 95% CI: −522, −104). The inverse association of erythrocyte Cd above 0.50 μg/kg with birth length was similar to that of the entire group, but no longer statistically significant (B: −0.74; 95% CI: −1.6, 0.16). The associations with erythrocyte Cd below 0.50 μg/kg appeared to be positive for both birth weight and birth length and were statistically significant in relation to birth weight among never-smokers (B: 78; 95% CI: 9.9, 146). The associations between urinary Cd (log_2-transformed) and birth anthropometry measures were mostly inverse, but no association was statistically significant.

In multivariable-adjusted linear regression models, maternal erythrocyte Pb (log_2-transformed) was consistently inversely associated with birth weight and length, but the associations were non-significant. In the spline regression model of erythrocyte Pb with head circumference, we found an inverse association above the spline knot (14 μg/kg), although not statistically significant. In the sub-group analyses of never-smokers, the associations were similar to those of all mothers (Table 2).

In multivariable-adjusted spline regression models for Hg, a doubling of maternal erythrocyte Hg (log_2-transformed) above 1.0 μg/kg was associated with a mean decrease in birth weight by −59 g (95% CI: −115, −3.0), and in birth length by −0.29 cm (95% CI: −0.54, −0.047). Maternal erythrocyte Hg above 0.76 μg/kg was also inversely associated with head circumference, although the association was not statistically significant (B: −0.14; 95% CI: −0.29, 0.0056). Below 1.0 μg/kg, a doubling of maternal erythrocyte Hg was associated with a mean increase in birth weight by 58 g (95% CI: 11, 105) and in birth length by 0.24 cm (95% CI: 0.023, 0.45). Additionally adjusting the association between maternal Hg and birth weight for maternal fish consumption (n = 533) had little impact; the inverse association above the knot (B: −71; 95% CI: −130, −11) was slightly increased compared to that of the same mothers without adjustment for fish consumption (B: −63; 95% CI: −121, −5.4), while the positive association below the spline knot (B: 52; 95% CI: 2.9, 101) was slightly attenuated compared to that of the same mothers (n = 533) without adjusting for fish intake (B: 58; 95% CI: 10, 105). For birth length, the inverse association became slightly more pronounced after further adjustment for

Table 2
Multivariable-adjusted linear and spline regression analyses of maternal metal concentrations (log_2-transformed) in urine and erythrocytes in pregnancy with infant birth anthropometry.

Outcome	All mothers					Never-smokers			
	n	B	95%CI	p	p_{sex}	B	95%CI	p	p_{sex}
Birth weight									
Ery-Cd<0.50 μg/kg	479	63	(-1.4, 128)	0.082	0.60	**78**	**(9.9, 146)**	**0.025**	0.35
Ery-Cd>0.50 μg/kg	79	**−191**	**(-315, -68)**	**0.002**	0.24	**−313**	**(-522, -104)**	**0.003**	0.087
U–Cd (linear)	555	−6.1	(-50, 38)	0.79	0.37	−2.5	(-48, 43)	0.91	0.33
Ery-Pb (linear)	558	−13	(-66, 41)	0.64	0.88	−19	(-73, 35)	0.50	0.70
Ery-Hg<1.0 μg/kg	150	**58**	**(11, 105)**	**0.015**	0.31	**53**	**(3.7, 102)**	**0.035**	0.38
Ery-Hg>1.0 μg/kg	408	**−59**	**(-115, -3.0)**	**0.039**	0.62	**−59**	**(-116, -2.7)**	**0.040**	0.50
Birth length									
Ery-Cd<0.50 μg/kg	466	0.11	(-0.17, 0.39)	0.43	0.87	0.11	(-0.19, 0.40)	0.48	0.96
Ery-Cd>0.50 μg/kg	79	**−0.67**	**(-1.2, -0.14)**	**0.014**	0.50	−0.74	(-1.6, 0.16)	0.11	0.48
U–Cd (linear)	542	0.002	(-0.19, 0.19)	0.99	0.34	0.018	(-0.18, 0.21)	0.86	0.64
Ery-Pb (linear)	545	−0.080	(-0.31, 0.15)	0.50	0.43	−0.096	(-0.33, 0.14)	0.42	0.68
Ery-Hg<1.0 μg/kg	148	**0.24**	**(0.023, 0.45)**	**0.030**	0.57	0.22	(-0.002, 0.45	0.052	0.75
Ery-Hg>1.0 μg/kg	397	**−0.29**	**(-0.54, -0.047)**	**0.020**	0.69	**−0.31**	**(-0.56, -0.057**	**0.016**	0.88
Head circumference									
Ery-Cd (linear)	545	0.002	(-0.14, 0.15)	0.98	0.94	0.067	(-0.096, 0.23)	0.42	0.66
U–Cd (linear)	542	−0.022	(-0.15, 0.11)	0.74	0.92	−0.008	(-0.14, 0.12)	0.90	0.89
Ery-Pb<14 μg/kg	378	0.059	(-0.22, 0.34)	0.68	0.84	0.056	(-0.24, 0.35)	0.71	0.66
Ery-Pb>14 μg/kg	167	−0.24	(-0.53, 0.056)	0.11	0.23	−0.23	(-0.53, 0.063)	0.12	0.20
Ery-Hg<0.76 μg/kg	101	0.12	(-0.045, 0.29)	0.15	0.72	0.14	(-0.036, 0.32)	0.12	0.65
Ery-Hg>0.76 μg/kg	444	−0.14	(-0.29, 0.006)	0.059	0.21	−0.14	(-0.29, 0.007)	0.062	0.11

Abbreviations: CI, confidence interval; Ery-Cd, erythrocyte cadmium; Ery-Hg, erythrocyte mercury; Ery-Pb. Erythrocyte lead; U–Cd, urinary cadmium; p_{sex}, p for interaction with infant sex.
[a]Adjusted for gestational age (days), infant sex, maternal early-pregnancy BMI, maternal education (2 groups; high school or lower, and university), pre-pregnancy smoking (never/ever).
[b]Adjusted as for all mothers with the exception of maternal pre-pregnancy smoking as only never-smokers were included.

maternal fish consumption (B: −0.38; 95% CI: −0.64, −0.12; n = 521) compared to that of the same mothers without adjustment for fish consumption (B: −0.35, 95% CI: −0.61; −0.092; n = 521). The inverse association with head circumference above the spline knot was essentially unaffected (B: −0.16; 95% CI: −0.32, −0.006; the same mothers without adjustment for fish intake: B: −0.15, 95% CI: −0.30, −0.0033; n = 521).

We observed no statistically significant interactions between infant sex and any of the metals in relation to any of the outcomes (p_{sex}>0.05; Table 2).

3.4. Mutually adjusted metal exposure in pregnancy and infant birth anthropometry

In the multivariable-adjusted models including mutual adjustment for all erythrocyte exposure biomarkers (Table 3), the inverse associations of maternal erythrocyte Cd above 0.50 μg/kg with birth weight and length remained, with similar unstandardized estimates for birth weight (B: −184 g; 95% CI: −307, −61) and birth length (B: −64 cm; 95% CI: −1.2, 0.11) as in the model with only erythrocyte Cd (B: −191 g; 95% CI: −315, −68; B: −0.67 cm; 95% CI: −1.2, −0.14, respectively; Table 2). Erythrocyte Cd above 0.50 μg/kg also had the strongest standardized estimates for both birth weight and length (β: −0.11; 95% CI: −0.19, −0.037; β: −0.096; 95% CI: −0.18, −0.017, respectively). The most pronounced association with head circumference was observed with erythrocyte Hg above 0.76 μg/kg, and the unstandardized estimate (B: −0.13 cm; 95% CI: −0.20, 0.025) was similar to that in the model with Hg only (B: −0.14 cm; 95% CI: −0.29, 0.006). For all mutually adjusted models, the VIFs were below 2.

3.5. Bayesian kernel machine regression

The Bayesian kernel machine regression suggested inverse associations of erythrocyte Cd (centered and scaled) with birth weight and birth length, although the confidence intervals were wide for all associations (Figs. S4A–C). Inverse associations were also suggested for erythrocyte Hg in relation to all three outcomes, and erythrocyte Pb appeared to mainly be inversely associated with head circumference. We observed no indication of interactions between the three metals in relation to birth anthropometry (Figs. S5A–C), or any indication of joint effects on the studied outcomes from mixed exposure to Cd, Pb, and Hg (Figs. S6A–C).

3.6. Maternal metal exposure in pregnancy and being born small-for-gestational age

The results from the logistic regression analyses of the child being born small-for-gestational age in relation to maternal metal concentrations are presented in Table 4. In the analysis of small-for-gestational age according to the ultrasound-based growth curves and classified as below mean −2 SD (Marsal et al., 1996), the odds ratios for erythrocyte and urinary Cd appeared to increase across the exposure tertiles, but no association was statistically significant (p for trend 0.29 and 0.086 for erythrocyte and urinary Cd, respectively). In the analyses of small-for-gestational age according the population-based growth curves (Skjaerven et al., 2000), the odds ratio of being small-for-gestational age (<10th percentile) was 2.2 (95% CI: 1.0, 4.6; p for trend 0.020) when comparing children of mothers in the highest Hg exposure tertile with those in the lowest. Using the customized growth curves (Gardosi et al., 1992) and classification of small-for gestational age as <10th percentile, no consistent or statistically significant association was observed for any of the metals.

4. Discussion

The present study indicates that even low-level maternal exposure to Cd and Hg during pregnancy might negatively affect birth weight and length. Noteworthy, all associations were non-linear (inverted U-shape), possibly related to nutritious food being the main sources of exposure. We found that the mothers' Cd exposure was mainly related to their intake of plant derived foods. As anticipated, Hg exposure was most prominently associated with

Table 3
Multivariable-adjusted linear and spline regression analyses of mutually adjusted maternal metal concentrations (log_2-transformed) in erythrocytes in pregnancy with infant birth anthropometry.

Outcome	Unstandardized estimates		Standardized estimates		
	B	95%CI	β	95%CI	p
Birth weight					
Ery-Cd<0.50 μg/kg	**66**	**(1.2, 131)**	**0.072**	**(0.0013, 0.14)**	**0.046**
Ery-Cd>0.50 μg/kg	**−184**	**(-307, -61)**	**−0.11**	**(-0.19, -0.037)**	**0.003**
Ery-Pb	−7.4	(-62, 47)	−0.0091	(-0.077, 0.058)	0.79
Ery-Hg<1.0 μg/kg	**56**	**(9.1, 102)**	**0.085**	**(0.014, 0.16)**	**0.019**
Ery-Hg>1.0 μg/kg	**−57**	**(-114, -0.29)**	**−0.073**	**(-0.15, -0.0004)**	**0.049**
Birth length					
Ery-Cd<0.50 μg/kg	0.13	(-0.15, 0.41)	0.035	(-0.039, 0.11)	0.36
Ery-Cd>0.50 μg/kg	**−0.64**	**(-1.2, -0.11)**	**−0.096**	**(-0.18, -0.017)**	**0.018**
Ery-Pb	−0.026	(-0.26, 0.21)	−0.0078	(-0.079, 0.064)	0.83
Ery-Hg<1.0 μg/kg	**0.23**	**(0.013, 0.44)**	**0.080**	**(0.0045, 0.16)**	**0.038**
Ery-Hg>1.0 μg/kg	**−0.28**	**(-0.54, -0.033)**	**−0.088**	**(-0.17, -0.010)**	**0.027**
Head circumference					
Ery-Cd	0.012	(-0.13, 0.16)	0.0061	(-0.067, 0.079)	0.87
Ery-Pb<14 μg/kg	0.068	(-0.22, 0.35)	0.018	(-0.058, 0.094)	0.64
Ery-Pb>14 μg/kg	−0.20	(-0.49, 0.10)	−0.050	(-0.13, 0.026)	0.19
Ery-Hg<0.76 μg/kg	0.11	(-0.054, 0.28)	0.051	(-0.024, 0.13)	0.18
Ery-Hg>0.76 μg/kg	−0.13	(-0.27, 0.025)	−0.065	(-0.14, 0.013)	0.10

Abbreviations: CI, confidence interval; Ery-Cd, erythrocyte cadmium; Ery-Hg, erythrocyte mercury; Ery-Pb. Erythrocyte lead; U–Cd, urinary cadmium.
[a]Adjusted for gestational age (days), infant sex, maternal early-pregnancy BMI, maternal education (2 groups; high school or lower, and university), pre-pregnancy smoking (never/ever).

Table 4
Multivariable-adjusted logistic regression analyses of maternal metal concentrations (μg/kg; categorized into tertiles) in erythrocytes and urine in pregnancy in relation to infants born small for gestational age.

Outcome	Tertile	Ery-Cd % Cases (n)	OR	95%CI	p	p for trend	U–Cd % Cases (n)	OR	95%CI	p	p for trend	Ery-Pb % Cases (n)	OR	95%CI	p	p for trend	Ery-Hg % Cases (n)	OR	95%CI	p	p for trend
Ultrasound based growth curves																					
All mothers[a]	1	0.53 (1)	Ref				0.54 (1)	Ref				1.1 (2)	Ref				2.2 (4)	Ref			
	2	2.2 (4)	3.48	(0.38, 32)	0.27		1.6 (3)	3.77	(0.38, 37)	0.26		2.2 (4)	2.11	(0.38, 12)	0.40		1.1 (2)	0.61	(0.11, 3.5)	0.58	
	3	2.2 (4)	3.90	(0.41, 37)	0.24	0.29	2.7 (5)	6.32	(0.71, 56)	0.099	0.086	1.6 (3)	1.68	(0.27, 10)	0.58	0.88	1.6 (3)	1.06	(0.21, 5.2)	0.95	0.91
Never-smokers[b]	1	0.55 (1)	Ref				0.56 (1)	Ref				0.57 (1)	Ref				1.9 (3)	Ref			
	2	2.2 (4)	3.49	(0.38, 32)	0.27		1.7 (3)	3.84	(0.39, 38)	0.25		2.3 (4)	4.37	(0.48, 40)	0.19		1.1 (2)	0.67	(0.11, 4.1)	0.66	
	3	1.9 (3)	3.59	(0.36, 35)	0.27	0.34	2.4 (4)	5.24	(0.57, 48)	0.15	0.15	1.7 (3)	3.06	(0.31, 30)	0.34	0.81	1.6 (3)	1.19	(0.23, 6.2)	0.84	0.79
Population based growth curves																					
All mothers[a]	1	16 (8.6)	Ref				17 (9.2)	Ref				13 (7.0)	Ref				13 (7.0)	Ref			
	2	15 (8.1)	0.89	(0.42, 1.9)	0.76		18 (9.7)	1.17	(0.58, 2.4)	0.66		20 (11)	1.65	(0.79, 3.4)	0.19		12 (6.5)	0.97	(0.42, 2.2)	0.94	
	3	19 (10)	1.21	(0.59, 2.5)	0.60	0.53	16 (8.7)	1.14	(0.55, 2.4)	0.73	0.76	17 (9.2)	1.45	(0.67, 3.1)	0.34	0.74	25 (13)	**2.16**	**(1.0, 4.6)**	**0.043**	**0.020**
Never-smokers[b]	1	15 (8.2)	Ref				17 (9.5)	Ref				12 (6.9)	Ref				10 (6.2)	Ref			
	2	15 (8.3)	0.99	(0.46, 2.1)	0.97		18 (11)	1.25	(0.61, 2.5)	0.54		18 (11)	1.58	(0.73, 3.4)	0.24		12 (6.8)	1.18	(0.49, 2.9)	0.71	
	3	17 (11)	1.34	(0.64, 2.8)	0.44	0.40	13 (7.7)	0.96	(0.44, 2.1)	0.92	0.86	17 (9.6)	1.49	(0.68, 3.3)	0.32	0.63	25 (14)	**2.57**	**(1.2, 5.7)**	**0.020**	0.009
Customized growth curves																					
All mothers[a]	1	31 (17)	Ref				27 (15)	Ref				25 (14)	Ref				32 (18)	Ref			
	2	24 (13)	0.75	(0.42, 1.4)	0.34		34 (19)	1.24	(0.71, 2.2)	0.45		33 (18)	1.36	(0.77, 2.4)	0.29		26 (14)	0.84	(0.47, 1.5)	0.55	
	3	33 (18)	1.05	(0.60, 1.9)	0.86	0.72	28 (15)	0.99	(0.55, 1.8)	0.98	0.86	30 (16)	1.25	(0.70, 2.2)	0.45	0.78	30 (16)	1.09	(0.61, 1.9)	0.77	0.68
Never-smokers[b]	1	30 (17)	Ref				27 (15)	Ref				21 (12)	Ref				24 (15)	Ref			
	2	23 (13)	0.76	(0.41, 1.4)	0.37		31 (18)	1.29	(0.72, 2.3)	0.39		30 (18)	1.53	(0.83, 2.8)	0.17		25 (14)	0.97	(0.52, 1.8)	0.92	
	3	26 (16)	1.06	(0.59, 1.9)	0.85	0.74	22 (13)	0.89	(0.48, 1.7)	0.72	0.62	28 (16)	1.34	(0.72, 2.5)	0.36	0.79	30 (16)	1.24	(0.68, 2.3	0.49	0.43

Abbreviations: CI, confidence interval; Ery-Cd, erythrocyte cadmium; Ery-Hg, erythrocyte mercury; Ery-Pb, Erythrocyte lead; OR, odds ratio; Ref, reference tertile; SGA, small-for-gestational age; U–Cd, urinary cadmium.
[a] Adjusted for maternal early-pregnancy BMI, maternal education (2 groups; high school or lower, and university), pre-pregnancy smoking (never/ever).
[b] Adjusted as for all mothers with the exception of maternal pre-pregnancy smoking as only never-smokers were included.

intake of fish and shellfish. The biomarker concentrations of Cd, Pb, and Hg were not strongly correlated, and the BKMR analyses did not indicate any interactions between the metals, or any non-additive effects of mixed exposure, in relation to birth anthropometry. There were no clear associations between maternal metal exposure and the odds of the child being born small for gestational age, however, statistical power was low.

The median maternal erythrocyte Cd concentration was 0.29 μg/kg (corresponding to whole blood Cd of about 0.11 μg/L, range: 0.02–2.2 μg/L; Table S5), but only the erythrocyte Cd concentrations above 0.50 μg/kg (around 0.20 μg/L in whole blood) were inversely associated with birth weight and length. This is in support of findings in a large previous study of 4191 mother-child dyads in the U.K, in which slightly higher maternal blood Cd concentrations (median: 0.29 μg/L; range: 0.14–6.3 μg/L) were inversely associated with birth weight and length (Taylor et al., 2016). Similarly, in a study of 1027 mother-child dyads in the U.S., birth weight percentiles by gestational age were found to decrease across tertiles of maternal blood Cd (median: 0.40 μg/L; lowest tertile: ≤0.28 μg/L; highest tertile: ≥0.50 μg/L) (Johnston et al., 2014). Importantly, the present study found that the inverse association of maternal erythrocyte Cd above 0.50 μg/kg with birth weight and length remained among never-smokers, which was also shown for non-smokers in the U.K study (Taylor et al., 2016). This is an important finding as smoking is associated with additional Cd exposure (Elinder et al., 1983), as well as decreased size at birth (Pereira et al., 2017). Thus, the associations in never-smokers would be more exclusively related to dietary Cd. In contrast to earlier studies indicating that girls are more sensitive to Cd exposure than boys (Kippler et al., 2012; Taylor et al., 2016), we found no indications of an interaction with the infants' sex, which may potentially be related to low statistical power.

A recent meta-analysis found maternal urinary Cd to be inversely associated, although non-significantly, with birth weight (Khoshhali et al., 2019). We also measured maternal urinary Cd concentrations, but these were not associated with the birth outcomes. The likely reason is that urinary Cd reflects the life-long exposure (Akerstrom et al., 2013; Amzal et al., 2009), rather than the exposure during pregnancy, as blood Cd does. Cadmium exposure during pregnancy leads to a marked accumulation of Cd in the placenta (Kippler et al., 2010; Kopp et al., 2012), where the strong pro-oxidant effects of Cd may cause impaired placental function (Everson et al., 2019; Geng and Wang, 2019; Thompson and Al-Hasan, 2012; Vilahur et al., 2015) that might compromise transport of nutrients to the fetus (Kippler et al., 2010; Tekin et al., 2012; Wier et al., 1990). Previous studies have found a moderate correlation between Cd concentrations in maternal blood and placenta (Fagerstedt et al., 2015), why we might have found stronger associations with birth outcomes had we measured Cd in placenta. The available limited studies on Cd in placenta and birth anthropometry (Khoshhali et al., 2019; Mazurek et al., 2019; Punshon et al., 2019) are inconclusive, and it cannot be excluded that even small amounts of Cd passing to the fetus (Kippler et al., 2013) may have negative effects on embryonic and fetal development (Thompson and Bannigan, 2008).

The mothers' Cd concentrations were positively associated with intake of root vegetables and vegetables, grains, rice, and nuts and seeds, which are all known sources of Cd (EFSA, 2012a). Consequently, we found markedly higher erythrocyte Cd concentrations among mothers with a lacto-ovo vegetarian diet than among those who consumed a mixed diet with meat and fish (median concentrations 0.50 and 0.29 μg/kg, respectively). In fact, Cd exposure was inversely associated with intake of red meat. This may be related to the fact that more Cd is absorbed when iron levels are low (Akesson et al., 2002; Kippler et al., 2007) and that consumption of red meat

is associated with increased intake of heme iron, which has high bioavailability (Hallberg, 1981). It could also be related to increased consumption of cereals and vegetables among individuals who do not eat meat. Soy products have previously been associated with higher Cd intake (Adams et al., 2011; Koseckova et al., 2020). Indeed, the few mothers who reported any consumption of soy-based foods had higher erythrocyte Cd than the mothers reporting no consumption.

Several previous studies have reported total Hg concentrations in maternal blood during pregnancy (Kobayashi et al., 2019; Lee et al., 2010) or in umbilical cord blood (Ballester et al., 2018, Lee et al., 2010; Ramon et al., 2009; Tatsuta et al., 2017) to be inversely associated with birth anthropometry, although at somewhat higher blood Hg concentrations (range of geometric mean values: 3.3–10 μg/L in whole blood) than in the present study. We found no studies that specifically related MeHg concentrations with pregnancy outcomes. In the present study, maternal erythrocyte Hg concentrations above 1.0 μg/kg (corresponding to about 0.40–4.3 μg Hg/L in whole blood; Table S5), which 73% of the women had, were inversely associated with weight and length at birth. At the lowest Hg exposure levels in our study, positive effects of essential nutrients in fish on fetal growth (Rogers et al., 2004) possibly outweighed a negative impact of the MeHg contamination of the fish (Strain, 2014). The total Hg concentration in erythrocytes is indeed a suitable biomarker of MeHg exposure, since over 90% of the MeHg in blood is found in the erythrocyte fraction, while the normally lower concentration of inorganic Hg is about equally distributed between plasma and erythrocytes (Berglund et al., 2005; Clarkson and Magos, 2006). Still, we cannot completely exclude that a small part of the Hg in erythrocytes was in the form of inorganic Hg. Most likely very few women had dental amalgam, a main source of inorganic Hg in the human circulation (Bjornberg et al., 2005; Clarkson and Magos, 2006), as dental amalgams were gradually phased out in Sweden already in the 1990's and was almost completely banned in 2009. Another source of inorganic Hg is food (mainly Hg^{2+}), although the intake in Europe is below the provisional tolerable weekly intake of 4 μg/kg body weight (EFSA, 2012b), and the intestinal absorption of this Hg form is low (Clarkson and Magos, 2006).

Although predatory lean fish usually contain elevated MeHg, erythrocyte Hg was associated with both lean and fatty fish. Probably, this was because most women ate mixed types of fish, in line with the dietary recommendations to pregnant women by the Swedish National Food Agency. Also, there was a very low prevalence of freshwater fish consumption (less than 3% of the women). Besides the observed relationship with fish and shellfish intake, erythrocyte Hg also appeared to be a marker of a healthy life-style as it increased with increasing intake of root vegetables, vegetables, eggs, and nuts and seeds, while it decreased with increasing intake of refined grains and chocolate. This finding is supported by our previous findings, showing two distinct life style-diet clusters among the present mothers, where higher education and higher age were clustered together with a diet rich in fruit, vegetables, and fish, while pre-pregnancy smoking and higher BMI was clustered together with a diet higher in fast foods, soft drinks, candy, and snacks (Stravik et al., 2019). That fish consumption increases with socioeconomic status and level of education has also been reported for other study populations, such as from the U.K. (Nykjaer et al., 2019).

Unlike Cd, MeHg is not accumulating in the placenta, but is actively transported to the fetus through e.g. the neutral amino acid transporters, as the MeHg-cysteine complex mimics methionine (Aschner and Clarkson, 1988; Kajiwara et al., 1996), and possibly also through the ABC transporters (Llop et al., 2014). Like Cd, on the other hand, MeHg is a potent inducer of reactive oxygen species (Valko et al., 2005), which has been associated with intra-uterine growth restriction (Kamath et al., 2006). In addition, it has been suggested that both MeHg and the other studied metals, even at low exposure levels, may interfere with steroid hormone activity or the hypothalamic-pituitary-thyroid axis (Georgescu et al., 2011; Iavicoli et al., 2009); key hormonal systems for fetal growth. Also, there is increasing evidence that early-life exposure to the metals is related to epigenetic alterations (Appleton et al., 2017; Bommarito et al., 2017; Kippler et al., 2013).

The more pronounced correlations between the dietary items and erythrocyte concentrations of Hg compared to those of Cd and Pb, are likely due to the much higher rate of gastrointestinal absorption of MeHg (>80%, compared with a few % for Cd and Pb) and the many factors that influence the absorption of Cd and Pb. For instance, the uptake of especially Cd, to some extent also Pb, increases at low iron stores and by pregnancy as such (Akesson et al., 2002; Meltzer et al., 2010), and the uptake of Pb increases by low calcium intake and fasting (EFSA, 2010). The mothers' Pb exposure, although generally very low, increased with increasing intake of game meat, which is in accordance with earlier Swedish and Norwegian studies (Birgisdottir et al., 2013; Bjermo et al., 2013; Wennberg et al., 2017), and a result of ammunition derived Pb contamination (Green and Pain, 2019). In accordance with other studies in Sweden and France (Tagne-Fotso et al., 2016; Wennberg et al., 2017), the mothers' Pb exposure increased with increasing consumption of coffee and/or tea. Some types of coffee contain significant levels of Pb (Nedzarek et al., 2013), and Pb may also leak from coffee machines (Muller et al., 2015) and water pipes (EFSA, 2010).

The main strengths of this study include the prospective design and the individual exposure assessment of the metals using suitable exposure biomarkers measured with a highly sensitive ICP-MS method in our laboratory. Even though we observed low metal concentrations, only two samples had a concentration below the LOD for Hg, while Pb and Cd could be detected in all samples. A major limitation is that we did not speciate Hg in the erythrocytes, and therefore we cannot exclude potential influence of inorganic Hg on the observed associations with birth anthropometry and maternal diet. Another limitation is that only around 10% of the total number of women (>6000) that delivered at Sunderby hospital during the study period participated in the study, and therefore they may not be representative of pregnant women in the area in general. The studied women seem to have higher education compared to all women giving birth at Sunderby hospital during 2015–2018 (Englund-Ögge et al., unpublished data), but the metal exposure appeared quite similar to that in southern Sweden (Akesson et al., 2002; Vahter et al., 2000). As with all observational studies, we cannot exclude that our findings are influenced by unmeasured or residual confounding, as possibly suggested by the positive associations with birth anthropometry observed at the lower metal concentrations. We had no information on the mothers' iron status, which may affect both the gastrointestinal uptake of Cd (Akesson et al., 2002; Meltzer et al., 2010) and fetal growth (Scholl, 2011). However, the increase in uptake of Cd starts already at slightly decreasing iron stores (measured as serum ferritin) and occurs throughout pregnancy, while increased risk for low birth weight and preterm birth has mainly been related to overt iron deficiency anemia in early gestation (Scholl, 2011). Also, as hemoglobin levels are routinely measured at the antenatal clinics in Sweden, and iron supplements are prescribed in case of decreasing hemoglobin levels, we assume that very few of the women had iron deficiency anemia. Lastly, we have explored associations between several exposure biomarkers and outcomes, which may raise a concern for multiple testing. However, as the outcomes are correlated, applying Bonferroni correction would be

inappropriate (Rothman, 1990).

5. Conclusion

The present study showed that maternal erythrocyte Cd and Hg were associated with poorer birth anthropometry, even at low levels prevalent in most populations world-wide. Studies on fetal outcomes following low-level maternal exposure to Cd, Pb, and Hg are very scarce, and thus, our findings should be confirmed in further large prospective studies. The studied metals showed entirely different correlation patterns with dietary consumption, and therefore dietary recommendations to decrease overall toxic metal exposure will be complex. Consequently, the results stress the importance of decreasing food contamination.

CRediT authorship contribution statement

Klara Gustin: Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization. **Malin Barman:** Investigation, Data curation, Writing - review & editing, Project administration. **Mia Stråvik:** Software, Formal analysis, Data curation, Writing - review & editing, Visualization. **Michael Levi:** Investigation, Formal analysis. **Fiona Murray:** Writing - review & editing, Data curation, Project administration. **Bo Jacobsson:** Writing - review & editing. **Ann-Sofie Sandberg:** Writing - review & editing, Project administration, Funding acquisition. **Anna Sandin:** Project administration, Funding acquisition. **Agnes E. Wold:** Writing - review & editing, Project administration, Funding acquisition. **Marie Vahter:** Writing - review & editing, Project administration, Funding acquisition. **Maria Kippler:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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.envpol.2020.114986.

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