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Metal exposure in the Greenlandic ACCEPT cohort: follow-up and comparison with other Arctic populations

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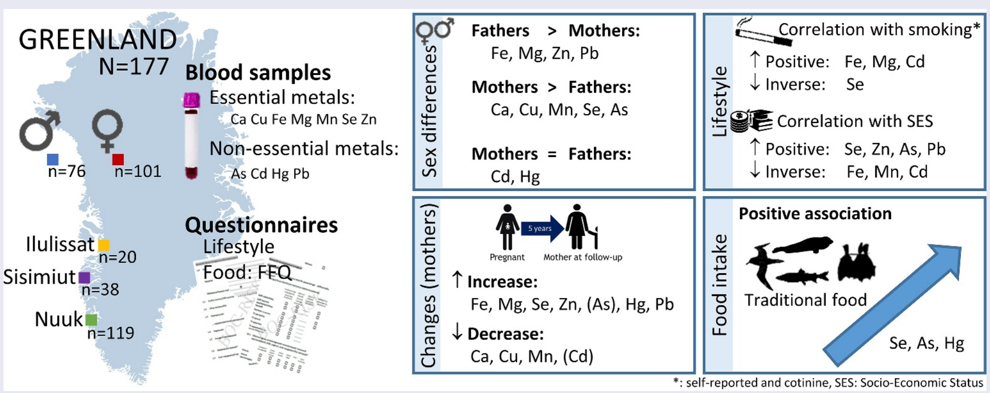
ABSTRACT

Humans are exposed to metals through diet and lifestyle e.g. smoking. Some metals are essential for physiologically body functions, while others are non-essential and can be toxic to humans. This study follows up on metal concentrations in the Greenlandic ACCEPT birth-cohort (mothers and fathers) and compares with other Arctic populations. The data from 2019 to 2020 include blood metal concentrations, lifestyle and food frequency questionnaires from 101 mothers and 76 fathers, 24–55 years, living in Nuuk, Sisimiut, and Ilulissat. A high percentage (25–45%) exceeded international guidance values for Hg. For the mothers, the metal concentrations changed significantly from inclusion at pregnancy to this follow-up 3–5 years after birth; some increased and others decreased. Most metals differed significantly between mothers and fathers, while few also differed between residential towns. Several metals correlated significantly with marine food intake and socio-economic factors, but the direction of the correlations varied. Traditional marine food intake was associated positively with Se, As and Hg. To the best of our knowledge, this study provides the most recent data on metal exposure of both men and women in Greenland, elucidating metal exposure sources among Arctic populations, and documents the need for continuing biomonitoring to follow the exceeding of guidance values for Hg.



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Background

Effects of metals on human health and disease are well documented [1]. The metals are generally classified as essential/beneficial or non-essential depending on their biological role in the human organism. The essential metals, including calcium (Ca), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), selenium (Se), and zinc (Zn) among others, are involved in physiologically important functions as integral components of enzymes or as a part of organic structures with vital functions [2,3]. Deficiencies of the essential metals may lead to several health effects, such as retarded growth, immune system disorders, hormone deficiency, and neuro system disorders [3,4]. However, some essential metals have the potential to turn harmful at high levels of exposure, e.g. Se and Zn [5,6]. Other metals such as arsenic (As), cadmium (Cd), mercury (Hg), and lead (Pb)

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are non-essential, and can be toxic and lead to adverse health effects [7]. Due to the high degree of toxicity, As, Cd, Hg, and Pb are ranked as chemicals of major public health concern by the World Health Organization [8] and classified as "carcinogenic" or "possibly carcinogenic" to humans by International Agency for Research on Cancer [9–11]. Exposure to the non-essential metals have been associated with negative effects on foetal growth, child behaviour, brain development, neurological problems, heart rate, and blood pressure among Arctic populations [12–21].

The primary exposure sources to metals in the general population include diet, drinking water, and lifestyle-related behaviours, such as smoking. However, the main exposure source varies for the different metals and may vary between different populations as well. Few studies on the human exposure sources in Greenland and other Arctic regions are published [22–26], mostly focusing on non-essential metals and intake via the traditional food without including imported food items. Three-day duplicate portions collected in Greenland (2004–2006) revealed a Ca intake below the Nordic Nutritional Recommendations, while Fe and Se intake met or was above the recommendation, respectively [22]. Based on data from 1995 to 1996, Johansen et al. [23] found that intake of Atlantic cod muscle, kittiwake muscle, and seal muscle and liver were the main contributors to Se intake while seal liver and kidney were the main food contributors to Cd intake, and intake of seal muscle, liver and kidney were the main contributors to Hg intake (Table S1). The use of lead shot for hunting has previously been a source of Pb exposure in Greenland [27], however, use of lead shot has been forbidden in Greenland since 2014. Comprehensive data from Arctic Canada collected in 1997–2000 showed that white bread was the main contributor to Ca, caribou and seal meat to Fe, and caribou meat and beef to Zn. The major contributors to the non-essential metals were also assessed: intake of Arctic char was the main contributor to As; caribou meat, ringed seal meat and kidney to Cd; caribou meat, lake trout, and ringed seal meat and kidney to Hg; and caribou and Arctic char to Pb [24] (Table S1). More recent data collected in 2016 from Arctic Russia (Coastal Chukotka) showed that marine mammal meat was the main source for Zn, fish and seafood were the main traditional food sources for As, Cd, and Hg, fowl and land mammal meat were the main sources of Pb [25]. It must be noted that only intake of locally harvested food was included in the Russian study, and intake of metals via market food were not included [25] (Table S1). Furthermore, non-dietary sources were not included in any of the previous studies. Importantly, tobacco smokers are highly exposed to Cd causing up to five times higher Cd blood concentrations in tobacco smokers compared to non-smokers [28–30].

Previous assessments have identified Arctic populations to be at high risk of metal exposure due to consumption of traditional foods and particularly high Hg levels have been reported in Northwest and Eastern Greenland [31,32]. The dietary habits in Greenland have been in transition over the last century resulting in a lower intake of traditional food and a higher intake of imported western food. Today, the traditional food items are only around 12–21% of the total food intake, depending on residential place, sex, and age [22,33–36]. Thus, it has become more important to include imported food items in the exposure source assessment of metals and it is important to follow the time trend of metal levels in the changing Greenlandic population.

Methods

Study population

The study population is previously described [36]. This study is a follow-up on the ACCEPT birth cohort [33,34] established during 2010–2015 in Greenland. When the children were 3–5 years of age, we followed-up on 101 mothers, 76 fathers, and their ACCEPT children ($n = 102$) from May 2019 to January 2020. The study flowchart is shown in Figure S1. Of the 150 mothers fulfilling the follow-up inclusion criteria, 133 mothers were contacted, and 102 agreed to participate (one mother was contacted and agreed to participate twice as she participated with two children from independent pregnancies, thus 101 unique mothers were included). The child's biological father was not included at pregnancy, but, if possible, he was included in this follow-up. The participation rate at follow-up was 76.6%, and those who did not accept to participate mainly gave lack of time as the reason.

After receiving a detailed description of the study, all participants gave written informed consent to participate. The families got two home visits from a health nurse visitor and project researchers, respectively. At the first visit, the health nurse visitor interviewed the families and questionnaires were filled out, and at the second visit, project researchers collected biological samples (blood, hair, urine, and nails).

The Commission for Scientific Investigations in Greenland (KVUG 2019–04) approved the study.

Questionnaire data

At this follow-up, the adult participants completed a self-administered questionnaire in Danish or Greenlandic with the possibility of assistance by the health nurse visitor if the participants were in doubt about the meaning of the questions and possible answers. The details are previously described [36,37].

Data on age, history of living places (in- and outside of Greenland), ethnicity (Inuit (both parents Greenlandic), partly-Inuit (one Greenlandic parent), and non-Inuit (no Greenlandic parents), educational level, income, alcohol intake, smoking history, use of controlled substances (narcotic and non-narcotic illicit drugs), body mass index (BMI) (from self-reported height and weight), and number of children was extracted from this follow-up questionnaires. For smoker and former smokers, pack years were calculated as (cigarettes per day/20 cigarettes/pack) * years of smoking.

Data from the food frequency questionnaire (FFQ) from this follow-up is previously published [36]. Shortly, food frequency intake scores (times per month) were calculated for seven traditional food groups (Marine mammals, Seabirds, Fish, Dried fish, Shellfish, Terrestrial animals, and Berries) and seven imported food groups (Meat products, Carbohydrate foods, Sauce, Fruit, Vegetables, Fast food, and Sweets & Snacks) by summing the intake scores (times per month) from 42 traditional and 23 imported food items [36].

At inclusion of the mothers during pregnancy (2013–2015), they filled out similar questionnaires used in this follow-up containing information related to pregnancy lifestyle and diet, including age, pre-pregnancy BMI, parity, alcohol intake (before and during pregnancy), and smoking history (never, former, current) [34].

Measurement of metals

Metals were determined at Department of Ecoscience, Aarhus University, Roskilde, Denmark following methods previously described [38,39]. The following metals were measured in whole blood (WB): Ca, Cu, Fe, Mg, Mn, Se, Zn, As, Cd, Hg, and Pb. Selenium was also measured in plasma (p-Se). Mercury was determined by a direct combustion mercury analyser (DMA-80) [38]. All other metals were determined by inductively coupled plasma mass spectrometry following microwave-assisted acid digestion [39]. The certified reference materials Seronorm Whole Blood L-1 og L-2 og Seronorm Serum L-1 og L-2 were analysed with the samples for QA/QC and the recovery percentages were 84–118% for the metals above the limit of detection (LOD). The QA/QC results are provided in Table S2.

We include Se and As in the term "metals" throughout the manuscript, even though Se is not a metal (but an element) and As is a metalloid.

Measurement of fatty acids

Fatty acid (FA) compositions of total plasma phospholipid were determined at Lipid Analytical Laboratories Inc., Guelph, Canada as previously described [40,41]. Lipids were extracted from the plasma samples [42], and the plasma phospholipids were separated from the neutral lipids by thin-layer chromatography [40,41]. The FAs methyl esters were prepared from the isolated phospholipid fraction [43] and were analysed using gas–liquid chromatograph. The results were expressed as the percentage of total FAs in plasma and the ratio between *n*-3 and *n*-6 (*n*-3/n-6) FAs was calculated as a biomarker of marine food intake.

Cotinine

Serum cotinine was used as a biomarker for current smoking of tobacco. The cotinine concentrations were analysed in serum samples using the Calbiotech Cotinine Direct ELISA Kit (Calbiotech Inc., CA, USA) at Centre of Arctic Health & Molecular Epidemiology, Aarhus University in Denmark. For values below limit of detection (LOD) (1 ng/ml), we assigned the value 0.50 ng/mL (LOD/2).

Statistics

All statistical analyses were performed with SPSS software version 28 (SPSS Inc., Chicago, IL, USA). The statistically significant level was set to $p < 0.050$ and borderline significant level was set to $0.050 \leq p < 0.080$.

To comply with the general data protection regulation stating that a single value corresponding to a single participant cannot be reported, we present pseudo ranges and medians on information from at least five individuals who had values closest to the actual value.

All metals were above LOD in more than 90% of the samples. For samples below LOD, we assigned the samples with values of LOD/2 for the statistical analysis.

To reduce redundancy of the metal variables and remove possible multi-collinearity, a principal components analysis (PCA) was conducted on the metal concentrations. The suitability of PCA was assessed prior to analysis. Inspection of the correlation matrix showed that Mn, Pb, and Cd were not strongly correlated (correlation coefficient smaller than [0.3]) with any of the other metals, and they were excluded from the PCA. The first PCA revealed two principal components (PC) that had eigenvalues greater than one and which explained 32.4% and 27.2% of the total variance, respectively. Visual inspection of the scree plot also indicated that two components should be retained [44]. In addition, a two-component solution met the interpretability criterion. As such, two components were retained and presented in Table S3. The overall Kaiser–Meyer–Olkin (KMO) measure was 0.644 with individual KMO measures all greater than 0.350 (Table S3). Bartlett's test of sphericity was statistically significant ($p < 0.0005$), indicating that the data was likely factorable. A Varimax orthogonal rotation was employed to aid interpretability. The rotated solution exhibited a "simple structure" [45].

We checked the distribution of the continuous variables by Q–Q plots and when non-normal distribution was found variables were ln-transformed to improve the normality. Difference between two groups (e.g. sex) were tested with independent samples Student's t-test and linear regression upon adjustment for confounders. Differences between more than two groups (e.g. BMI groups) were tested with ANOVA and ANCOVA upon adjustment for confounders. When we observed significant differences between groups with ANONA or ANCOVA, Tukey HSD post hoc tests were used to further reveal specific differences between the groups. For categorical variables, Pearson's chi-square test was used to test the difference between groups.

Correlations between the metal concentrations were assessed with Pearson correlation on ln transformed variables. Correlations between exposure variables (single metals and PCs) and lifestyle and socioeconomic factors were analysed with Spearman correlation, as some variables were categorical and not suited for Pearson correlation.

Associations between exposure variables (single metals and PCs) and food intake were analysed with linear regression, metals as dependent variables and food intake as independent variable. We ensured that the assumptions for linear regression analyses were not violated. Linearity was assessed by partial regression plots and a plot of residuals against the predicted values. Independence of residuals was assessed by Durbin-Watson statistic. Homoscedasticity was assessed by visual inspection of a plot of residuals versus unstandardised predicted values. Multi-collinearity was assessed by tolerance values greater than 0.1 and variance inflation factor below 10. Furthermore, the assumption of normality was assessed by Q–Q plots. Based on a priori knowledge on covariates suspected to be related to food intake and metal concentrations, the following variables were included in the models: age (continuous), town (categorical), sex (categorical), BMI (categorical), educational level (categorical), house income (categorical), and smoking history (categorical) [19,46–49].

To assess exposure changes in metal concentrations for the mothers from inclusion at pregnancy (1. trimester) to this follow-up 3–5 years after birth (3.7–6.1 years between the blood samples), the individual differences were calculated by subtracting the concentration measured at inclusion from the concentration measured at follow-up, divided by the years between the two blood samples. Wilcoxon Signed Rank test (median equal to 0) was used to test changes from inclusion at pregnancy to follow-up (for mothers only) in exposure concentrations. Furthermore, we assessed the pairwise correlations from inclusion to follow-up for the mothers using Pearson correlations. We also calculated partial Pearson correlations by adjusting for different predictors of the exposure concentrations. The correlations between inclusion at pregnancy and follow-up of the mother were adjusted for factors known to influence the metal concentrations [19,46–49]: time between the two blood samples (continuous), change in education level (categorical; same level or higher level), change in household income (categorical; lower, same or higher level), change in smoking status (categorical; never in both collections, never to former/current, former in both collections, former to current, current to former, current in both collections), change in BMI (continuous), and change in parity (continuous).

Results

Characteristics of the study population

The characteristics of the participants (101 mothers/76 fathers) were published in Wielsøe et al. 2022 [37] and presented in Table S4. The mean age was 35.3 years, with the mothers being significantly younger (33.8 years) than the fathers (37.2 years). Most of the participants lived in Nuuk (67.2%), while 21.5% and 11.3% lived in Sisimiut and Ilulissat, respectively. The mothers and fathers also differed significantly in which region they had lived the longest and the ethnic background. These differences were mainly due to the follow-up criteria, as mothers had to have lived longest in either the Disko Bay or West region and being of Inuit/partly-Inuit descent. However, some fathers had lived longest in other regions (11.4%) or outside Greenland (7.1%) and were of non-Inuit descent (6.6%) (Table S4). More than 75% of the participants were either overweight or obese with no difference between mothers and fathers. Concerning the highest education level, around 21% of the participants finished primary school and 8% had a high-school education. A higher percentage of the fathers had finished education at technical college, while more mothers had a university degree. More fathers had an income higher than 250.000 DKK (~36,200 USD) per year, but the household income was similar for fathers and mothers (Table S4). Fathers and mothers did not differ in alcohol consumption or smoking history (Table S4), and the majority reported 0 drinks/week (54.5%) and being current smokers (48.6%). Generally, there was a good agreement between the self-reported smoking history and measured smoking biomarker, serum cotinine levels. However, 8% of never smokers and 17% of former smokers had detectable cotinine levels (above 1 ng/mL), whereas 8% of the current smokers had non-detectable levels (not shown). The *n*-3/n-6 FA ratio did not differ between fathers and mothers (Table S4)

Metal concentrations

Table 1 shows the detection frequencies and concentration of the measured metals. All metals were detected in 92–100% of the samples (Table 1).

Figure S2 shows the correlations between the metals. Ca and Cu were positively correlated with each other, but generally they correlated inversely with the other metals. Overall, we observed positive correlations between most metals; however, the strength and significance level varied. One exception was the correlation between Mn and p-Se, which showed a significant inverse correlation.

To reduce redundancy of the metal variables and remove possible multi-collinearity, we used a principal component analysis (PCA), which identified two principal components explaining 32.4% and 27.2% of the total variance (Table S3). Principal component (PC)-1 displayed strong loading factors for the non-essential metals (As and Hg) together with Se (WB-Se and p-Se), whereas PC-2 displayed strong loading factors for the essential metals (Ca, Cu, Fe, Mg, and Zn). Component loading factors, individual Kaiser–Meyer–Olkin (KMO) measures, and communalities of the rotated solution are presented in Table S3. Strong positive correlations were seen between PC-1 and WB-Se, p-Se, As, and Hg, while PC-2 correlated inversely with Ca and Cu and positively with Fe, Mg, Mn, Zn, and Pb (Figure S2).

Changes in metal concentrations from pregnancy to follow-up (mothers only)

Most metals elicited significant changes in concentrations from pregnancy to this follow-up study (median time between the blood samples were 5.1 years) (Table 2). We found significant decreases per year for the essential metals Ca, Cu, and Mn, while Fe, Mg, Se (WB and P), and Zn had increased significantly. The non-essential metals As, Hg, and Pb increased significantly per year, while Cd decreased significantly.

Pearson pairwise correlations for the mothers at inclusion and follow-up were significant and positive for Mg, Mn, WB-Se, Zn, As, Cd, Hg, and Pb with adjusted correlation coefficient ranging from 0.299 to 0.767 (Table 2).

Differences in metal concentrations in fathers and mothers

Most of the metals differed significantly in concentrations between fathers and mothers (Figure 1, Table S5). The concentrations were significantly higher in fathers for Fe, Mg, Zn, and Pb, while mothers had the highest concentrations of Ca, Cu, Mn, WB-Se, and As (borderline). The level of PC-2 (strongly correlated with for Ca, Cu, Fe, Mg, and Zn) was also higher in fathers than in mothers (Figure 1, Table S5).

Differences in metal concentrations by residential town

Significant differences between the residential towns were seen for Cu, Mg, WB-Se, As, Cd, Hg, and PC-1 strongly correlated with As, Hg, and Se (Figure 2, Table S6). In the post hoc tests, Cu was significantly lower in Sisimiut than in both Nuuk and Ilulissat. Mg and WB-Se were significantly higher in Sisimiut than Nuuk. Even though a significant difference was seen for As in the ANCOVA test, no significance was seen in the post hoc tests. Cd was significantly lower in Nuuk than in Sisimiut and Ilulissat, while Hg was significantly higher in Ilulissat than in Nuuk and Sisimiut. The PC-1 (As, Hg and Se) level was significantly higher in Ilulissat than Nuuk (Figure 2, Table S6).

Correlation of metal concentrations with lifestyle and socioeconomic factors

Table 3 displays correlations between metal concentrations and lifestyle and socioeconomic factors. We found significant or borderline significant correlations between the measured metals and age, BMI, *n*-3/n-6 FA ratio, educational level, personal and household income, alcohol intake, smoking history, and lifetime spent in Greenland.

Cd was very strongly correlated with smoking and cotinine levels. In additional analyses, the Cd concentration differed significantly by the smoking history with lowest levels in never smokers and the highest concentration in current smokers (Figure S3). Cd associated positively with pack years ((cigarettes per day/20 cigarettes/pack) * years of smoking) for both former

Table 1. Concentrations of metals for the total study population.

	LOD	Fathers ($n = 70$ [¤])				Mothers ($n = 92$)				All ($n = 162$)			
		% >LOD	Mean (SD)	Median (IQR)	Min-Max	% >LOD	Mean (SD)	Median (IQR)	Min-Max	% >LOD	Mean (SD)	Median (IQR)	Min-Max
Essential metals													
Ca (mg/L)	0.3 mg/L	100.0%	55.9 (3.66)	55.8 (4.66)	49.3–63.5	100.0%	60.7 (5.36)	61.0 (65.9)	52.5–72.9	100.0%	58.7 (5.26)	58.3 (6.29)	49.3–72.9
Cu (mg/L)	0.004 mg/L	100.0%	0.837 (0.101)	0.828 (0.109)	0.642–1.06	100.0%	1.03 (0.246)	0.952 (0.174)	0.755–1.80	100.0%	0.944 (0.218)	0.898 (0.166)	0.642–1.80
Fe (mg/L)	0.3 mg/L	100.0%	513 (32.9)	513 (34.5)	441–572	100.0%	440 (58.7)	451 (47.3)	281–500	100.0%	471 (61.1)	477 (67.5)	281–571
Mg (mg/L)	0.05 mg/L	100.0%	43.0 (4.70)	42.5 (5.37)	34.2–52.3	100.0%	39.4 (4.98)	40.3 (5.83)	27.5–48.1	100.0%	41.0 (5.15)	41.4 (6.26)	27.5–52.3
Mn (µg/L)	0.8 µg/L	100.0%	9.02 (2.42)	8.61 (2.47)	5.42–15.0	100.0%	11.3 (4.73)	9.93 (4.26)	4.49–24.1	100.0%	10.3 (4.05)	9.38 (3.53)	4.43–24.1
WB-Se (µg/L)	100 µg/L	97.1%	215 (104)	196 (79.5)	103–492	100.0%	246 (163)	201 (77.5)	129–743	98.8%	232 (141)	199 (81.1)	97.7–812
p-Se (µg/L)	1 µg/L	100.0%	94.3 (13.1)	94.7 (13.0)	70.4–122	100.0%	90.3 (12.1)	91.1 (13.6)	64.4–115	100.0%	92.0 (12.6)	92.7 (12.9)	62.6–125
Zn (mg/L)	0.09 mg/L	100.0%	5.86 (0.774)	6.01 (1.06)	4.31–7.09	100.0%	5.25 (0.849)	5.42 (1.16)	3.28–6.48	100.0%	5.52 (0.870)	5.60 (1.17)	3.24–7.09
Non-essential metals													
As (µg/L)	2.1 µg/L	92.9%	8.17 (6.82)	6.51 (4.46)	1.05–26.7	92.4%	9.35 (6.88)	7.27 (5.82)	1.05–28.8	92.6%	8.84 (6.86)	6.88 (5.37)	1.05–35.0
Cd (µg/L)	0.08 µg/L	98.6%	0.662 (0.666)	0.392 (0.792)	0.084–2.52	98.9%	0.629 (0.484)	0.458 (0.573)	0.099–1.91	98.8%	0.644 (0.568)	0.424 (0.719)	0.068–2.68
Hg (µg/L)	0.1 µg/L	100.0%	6.82 (8.19)	5.11 (6.27)	1.08–26.5	100.0%	6.06 (6.59)	4.24 (4.63)	0.699–27.0	100.0%	6.39 (7.31)	4.45 (5.32)	0.562–37.5
Pb (µg/L)	1.6 µg/L	100.0%	14.5 (7.54)	12.8 (9.07)	5.34–32.4	96.7%	10.3 (9.61)	7.79 (5.67)	1.48–41.2	98.1%	12.1 (8.99)	9.24 (7.71)	1.48–44.8
Principal components													
PC-1	n/a	n/a	−0.035 (0.981)	−0.054 (0.847)	−1.29; 6.41	n/a	0.026 (1.018)	−0.172 (0.919)	−1.24–7.15	n/a	0.000 (1.000)	−0.135 (0.828)	—1.29–7.15
PC-2	n/a	n/a	0.704 (0.529)	0.781 (0.714)	−1.16; 1.97	n/a	−0.520 (0.949)	−0.456 (0.994)	−6.94–0.851	n/a	0.000 (1.000)	0.121 (1.253)	—6.94–1.97

The metals were measured in whole blood (WB), whereas selenium was also measured in plasma (P). WB-Se: Whole blood Selenium; p-Se: plasma Selenium. LOD: Limit of detection; SD: Standard Deviation; IQR: interquartile range; n/a: not applicable; PC: principal component; PC-1 strongly correlated with As, Hg and Se (whole blood and plasma): PC-2 strongly correlated with Ca, Cu, Fe, Mg, and Zn. [¤]: Among fathers, data on p-Se is missing for two samples.

Table 2. Changes and correlations of metal concentrations for the mothers from inclusion to follow-up.

	Individual difference (Follow-up – Inclusion) per year							Unadjusted Pearson correlation between Inclusion and Follow-up concentrations			Adjusted Partial Pearson correlation between Inclusion and Follow-up concentrations		
	Change in concentration per year				Change in percentage per year								
	n (%)	Mean (SD)	Median (IQR)	p-value	Mean (SD)	Median (IQR)	p-value	n	*r*	p-value	n	*r*	p-value
Essential metals													
Ca (mg/L)	53 (52.0%)	−0.09 (1.90)	−0.41 (1.23)	**0.004***	2.42% (17.01)	−0.73% (1.90)	**0.004***	53 (52.0%)	0.173	0.216	29 (28.7%)	0.177	0.340
Cu (mg/L)	93 (91.2%)	−0.05 (0.06)	−0.06 (0.07)	**<0.001***	−3.19% (4.71)	−4.74% (5.40)	**<0.001***	93 (91.2%)	0.033	0.751	45 (44.5%)	0.020	0.892
Fe (mg/L)	93 (91.2%)	0.15 (18.98)	2.85 (11.42)	**0.006***	0.41% (3.56)	0.69% (2.73)	**0.004***	93 (91.2%)	−0.002	0.986	45 (44.5%)	0.021	0.890
Mg (mg/L)	53 (52.0%)	0.23 (0.84)	0.46 (0.99)	**0.005***	0.73% (1.94)	0.96% (2.57)	**0.003***	53 (52.0%)	0.517	**<0.001***	29 (28.7%)	0.663	**<0.001***
Mn (µg/L)	93 (91.2%)	−2.24 (2.47)	−2.59 (3.36)	**<0.001***	−5.87% (11.07)	−9.84% (9.45)	**<0.001***	93 (91.2%)	0.234	**0.024***	45 (44.5%)	0.323	**0.027***
WB-Se (µg/L)	93 (91.2%)	16.29 (14.09)	14.89 (12.37)	**<0.001***	12.39% (9.54)	12.10% (11.63)	**<0.001***	93 (91.2%)	0.780	**<0.001***	45 (44.5%)	0.767	**<0.001***
p-Se (µg/L)	93 (91.2%)	2.33 (5.09)	2.22 (5.09)	**<0.001***	5.56% (10.4)	2.96% (7.28)	**<0.001***	93 (91.2%)	−0.052	0.620	45 (44.5%)	−0.034	0.822
Zn (mg/L)	93 (91.2%)	0.10 (0.19)	0.11 (0.12)	**<0.001***	2.36% (3.24)	2.38% (2.55)	**<0.001***	93 (91.2%)	0.419	**<0.001***	45 (44.5%)	0.476	**<0.001***
Non-essential metals													
As (µg/L)	93 (91.2%)	0.29 (1.36)	0.06 (1.16)	0.084	17.05% (49.39)	0.78% (20.08)	**0.010***	93 (91.2%)	0.351	**<0.001***	45 (44.5%)	0.316	**0.030***
Cd (µg/L)	93 (91.2%)	−0.03 (0.11)	−0.01 (0.10)	**0.026***	1.19% (15.80)	−2.32% (15.26)	0.307	93 (91.2%)	0.590	**<0.001***	45 (44.5%)	0.407	**0.004***
Hg (µg/L)	93 (91.2%)	0.13 (1.02)	0.10 (0.63)	**0.030***	9.16% (21.31)	3.71% (20.42)	**0.002***	93 (91.2%)	0.604	**<0.001***	45 (44.5%)	0.589	**<0.001***
Pb (µg/L)	93 (91.2%)	0.33 (2.09)	0.13 (1.01)	0.091	8.76% (26.84)	1.74% (13.42)	**0.009**	93 (91.2%)	0.333	**0.001***	45 (44.5%)	0.299	**0.041***

The analyses were conducted on mothers only ($N = 101$) and the time between the blood samples at including and follow up was between 3.7–6.1 years (median of 5.1 years). The individual differences per year were calculated by subtraction of the concentration from inclusion from the concentration at follow-up and dividing by years between the two time points, thus a difference of zero (0) reflect equal no change per year in concentration from inclusion to follow-up, negative values reflect higher concentration at inclusion, and positive value reflect higher concentration at follow-up. The individual differences were tested with a Wilcoxon Signed Rank test, with median equals 0. Bold p-values and * indicates significant difference ($p < 0.050$). Pearson correlations between concentrations at inclusion and follow-up. Partial Pearson correlations were used with adjustment for time between the two blood samples, change in education level, change in household income, change in BMI, change in parity, and change in smoking status. The metals were measured in whole blood (WB), whereas selenium was also measured in plasma (P). WB-Se: Whole blood Selenium; p-Se: plasma Selenium; n (%): number of participants with information and percentages of the total number of participants in the group (N); SD: Standard Deviation; IQR: interquartile range; r: Pearson correlation coefficient.

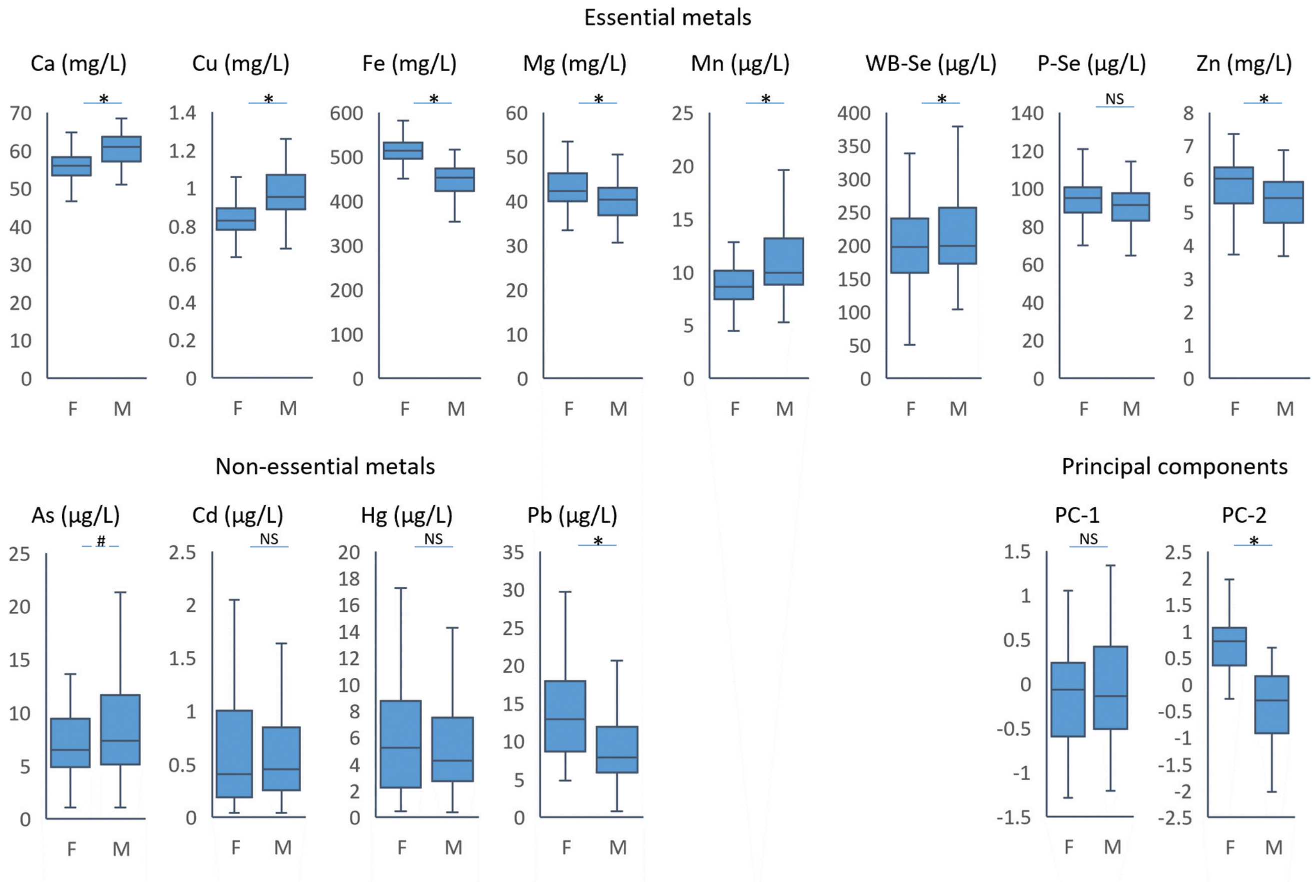

Figure 1. Concentrations of metals in fathers (F) and mothers (M).

Differences between fathers (F) and mothers (M) were tested by linear regression with adjustment for age and residential town on ln transformed variables. * and solid line indicate significant difference ($p < 0.050$) and # and dotted line indicate borderline significant difference (p: ≥0.050 and <0.080). NS: non-significant. The boxplots consist of the interquartile range (IQR) and the median (line inside the box), and whiskers are 1.5*IQR. Outliers are not included in the graphs (defined as values greater than 1.5*IQR). See Table S5 for concentrations and raw and adjusted p-values. The metals were measured in whole blood (WB), whereas selenium was also measured in plasma (P). WB-Se: Whole blood Selenium; p-Se: plasma Selenium; F: Fathers ($N = 76$). M: Mothers ($N = 101$). PC: principal components; PC-1 strongly correlated with As, Hg and Se (whole blood and plasma): PC-2 strongly correlated with Ca, Cu, Fe, Mg, and Zn.

smokers (ß (95% CI): 0.044 (0.009; 0.079), p = 0.015) and current smokers (ß (95% CI): 0.035 (0.011; 0.059), p = 0.004) (Figure S3). When stratified by the smoking history, Cd did only correlate significantly with cotinine levels in former and current smokers. As shown in Table S7, when stratified by smoking history, the significant correlations of Cd and *n*-3/n-6 FA ratio, educational level, personal income, and lifetime spent in Greenland observed in the non-stratified analysis disappeared, suggesting a confounding role of smoking history.

When stratified by sex, the correlations for fathers and mothers (Table S8) were generally like the overall correlations for the pooled dataset (Table 3 and Table S8), even though the significance level in some cases were lower in the stratified analyses due to lower sample number. However, some correlations differed substantially in strength and direction between the pooled analyses and the sex stratified analyses or between fathers and mothers (Table S8).

Metal concentrations associations with food intake

We analysed the associations between metal concentrations and intake of traditional Greenlandic and imported food groups. The unadjusted analyses are shown in Tables S9-S10, and the very similar results upon adjustment are shown in Tables 4–5. The significant findings in the adjusted analyses are described below.

For Fe, borderline significant inverse associations were seen with intake of dried fish and the summed traditional food group. Mn was associated inversely with shellfish. Concentrations of WB-Se, As, and Hg were associated positively with intake of marine

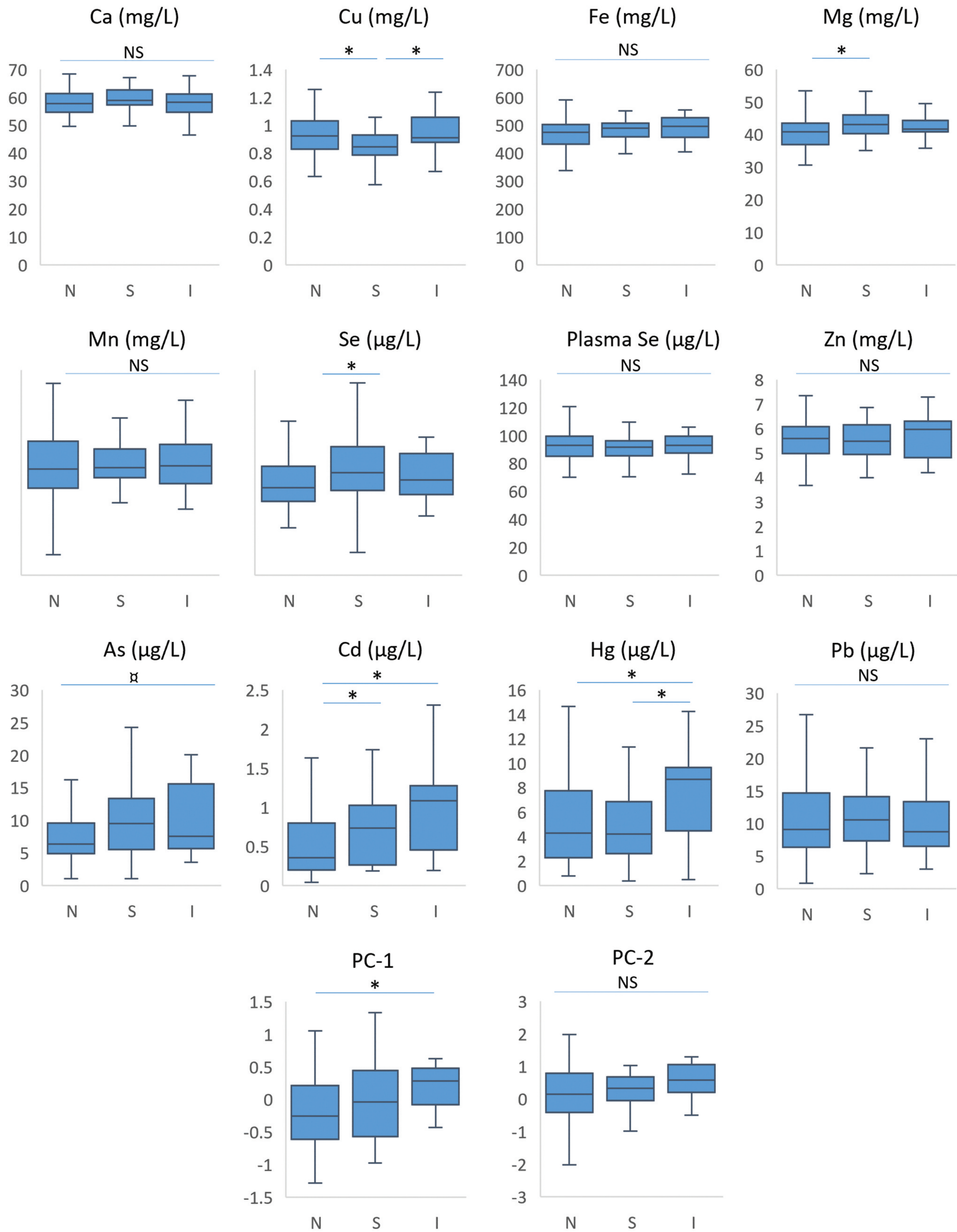

Figure 2. Concentrations of metals by residential town.

Differences between towns (Nuuk (N), Sisimiut (S), and Ilulissat (I)) were tested with ANCOVA on ln transformed variables adjusted for age and sex. If significant in the ANCOVA test, Tukey HSD post hoc test were used to test the specific differences between Nuuk and Sisimiut, Nuuk and Ilulissat, and Sisimiut and Ilulissat. NS: non-significant in the ANCOVA test. For the Tukey HSD post hoc test only the significant * ($p < 0.050$) and borderline mammals, seabirds, dried fish, and the summed traditional food group, while Zn associated inversely with the same food groups, except for marine mammals (Table 4). WB-Se was also associated positively with intake of terrestrial animals and Greenlandic fish, while As was associated positively with Greenlandic fish. In addition, p-Se was associated positively with intake of seabirds, Greenlandic fish, shellfish, and dried fish (Table 4).

Furthermore, PC-1 (mainly correlated with As, Hg, Se) was associated positively with intake of marine mammals, seabirds, Greenlandic fish, shellfish, dried fish, berries (borderline), and the summed traditional food group, while PC-2 (Ca, Cu, Fe, Mg, Zn) was associated inversely with intake of dried fish (Table 4).

We found few significant associations between the metal concentrations and intake of imported food groups (Table 5). Ca was associated inversely with vegetable intake, Mn was associated inversely with fruit, sweets & snack intake and the summed imported food group, p-Se was associated positively with fruit, sweets & snack, and summed imported food group (borderline), and Zn was associated positively with vegetable intake (Table 5). For the non-essential metals, Cd was associated positively with fast-food intake and Hg was associated inversely with intake of imported meat product (Table 5). For the PCs, PC-2 (Ca, Cu, Fe, Mg, and Zn) positive borderline significant associations were seen with vegetables and fruit intake (Table 5).

Discussion

We report concentrations of some essential (Ca, Cu, Fe, Mg, Mn, Se, Zn) and non-essential (As, Cd, Hg, Pb) metals in Greenlandic mothers and fathers participating in this ACCEPT follow-up data collection during 2019–2020. The intra-individual metal concentrations of the mothers changed significantly from inclusion at pregnancy (2013–15) to this follow-up study 3–5 years after birth; some were increased (Fe, Mg, Se, Zn, As, Hg, Pb) while others decreased (Ca, Cu, Mn, Cd). We found that a high percentage of the participants may be at risk of health effects related to Hg exposure as 25.3% and 45.0% exceeded the guidance values provided by Health Canada (8.0 µg/L) [50,51] and the German human biomonitoring Commission (5.0 µg/L) [52,53], respectively (Table 6). Most metals differed by sex (but not p-Se, Cd, and Hg), while some also differed by residential town (Cu, Mg, Se, As, Cd, Hg). Several metals correlated significantly with the marine food intake biomarker (*n*-3/*n-6* FA ratio) and the socio-economic factors (educational level and personal income), but the direction of the correlation varied. Some significant associations were found between food intake and metal concentrations, mainly for Se, Zn, As, Hg and the PC-1 which strongly correlated with As, Hg, and Se.

Comparison of metal concentrations among Arctic populations

There has been a special attention on biomonitoring of environmental contaminants in the Arctic populations during several decades [26,31,54–56], due to the intake of traditional food with high contaminant concentrations. Several publications and reports on blood metal concentrations from Arctic populations are available [26,31,54–56]. However, most studies have focused on the toxic metals, Hg, Pb, and Cd, as well as the essential element Se, and only few studies have included other metals. Within the Arctic region, previous reports generally found that the Hg concentration was highest in Greenland and Canada (Nunavik), Pb was highest in Canada (Yukon, Northwest Territories, and Nunavik), and As was highest in Greenland and Russia (Murmansk Oblast) [31].

In Table 7, we compare the metal concentrations measured in the present study with previous reports on metals in samples collected after 2010 in Greenland and other Arctic populations [19,26,32,57–65]. Differences in metal blood concentrations exist across Arctic populations, especially for Mn, As, Cd, Hg, and Pb where the concentrations differed by more than threefold across the reported studies in Table 7. Some of the variation could be due to differences in study designs in terms of populations (sex, age, etc.) and time point (even though we have limited to data from 2010). However, we expect that most of the variation may be explained by differences in dietary habits, exposure levels in the local animals and food, and lifestyle (e.g. smoking). We did see differences for most metals (except Ca, Fe, Mg, and Hg) between the pregnant ACCEPT women [19] and this follow-up 3–5 years after

significant # (p: ≥0.050 and <0.080) differences are indicated. ¤: Significant in the ANCOVA test, but no significant differences detected in the post-hoc test. The boxplots consist of the interquartile range (IQR) and the median (line inside the box), and whiskers are 1.5*IQR. Outliers are not included in the graphs (defined as values greater than 1.5*IQR). See Table S6 for concentrations and raw and adjusted p-values. The metals were measured in whole blood (WB), whereas selenium was also measured in plasma (P). WB-Se: Whole blood Selenium; p-Se: plasma Selenium; N: Nuuk. S: Sisimiut. I: Ilulissat. PC: principal components. PC-1 strongly correlated with As, Hg and Se (whole blood and plasma): PC-2 strongly correlated with Ca, Cu, Fe, Mg, and Zn.

Table 3. Spearman correlations between metal concentrations and lifestyle and socioeconomic factors.

	Age (year)	BMI (kg/m²)	*n*-3/n-6 FA ratio (indicator of marine food)	Educational level (categorical)[a]	Personal income (categorical)[b]	Household income (categorical)[c]	Alcohol intake (current, categorical)[d]	Smoking history (categorical)[e]	Smoking biomarker, Cotinine (ng/mL)	Lifetime spent in Greenland (%)
	r_s (95% CI)	r_s (95% CI)	r_s (95% CI)	r_s (95% CI)	r_s (95% CI)	r_s (95% CI)	r_s (95% CI)	r_s (95% CI)	r_s (95% CI)	r_s (95% CI)
Essential metals										
Ca (mg/L)	−0.102 (−0.257; 0.057)	**-0.283 (−0.437; −0.112)***	0.083 (−0.077; 0.239)	0.032 (−0.128; 0.190)	−0.141 (−0.302; 0.026)	−0.098 (−0.261; 0.070)	−0.177 (−0.356; 0.014)#	−0.003 (−0.162; 0.156)	−0.08 (−0.236; 0.081)	0.045 (−0.115; 0.203)
Cu (mg/L)	−0.023 (−0.181; 0.136)	−0.014 (−0.190; 0.162)	0.046 (−0.114; 0.203)	0.063 (−0.097; 0.220)	−0.165 (−0.323; 0.003)	0.058 (−0.111; 0.223)	0.031 (−0.161; 0.220)	−0.019 (−0.177; 0.140)	−0.075 (−0.232; 0.086)	0.095 (−0.065; 0.251)
Fe (mg/L)	0.054 (−0.106; 0.210)	**0.208 (0.033; 0.370)***	−0.074 (−0.230; 0.086)	**-0.172 (−0.323; −0.014)***	0.155 (−0.012; 0.314) #	−0.048 (−0.213; 0.120)	0.043 (−0.149; 0.232)	0.065 (−0.095; 0.221)	**0.174 (0.015; 0.325)***	−0.073 (−0.230; 0.087)
Mg (mg/L)	−0.062 (−0.219; 0.097)	0.149 (−0.028; 0.316)	**-0.166 (−0.317; −0.007)***	−0.145 (−0.297; 0.015) #	−0.052 (−0.217; 0.117)	−0.160 (−0.318; 0.008)#	−0.102 (−0.287; 0.091)	**0.171 (0.013; 0.321)***	**0.220 (0.063; 0.367)***	0.144 (−0.015; 0.296)#
Mn (µg/L)	−0.127 (−0.280; 0.032)	0.024 (−0.152; 0.199)	0.010 (−0.150; 0.168)	−0.080 (−0.236; 0.080)	**-0.235 (−0.387; −0.071)***	−0.054 (−0.219; 0.114)	**-0.190 (−0.368; 0.000)***	0.032 (−0.128; 0.189)	−0.034 (−0.193; 0.126)	0.064 (−0.096; 0.221)
WB-Se (µg/L)	0.085 (−0.075; 0.240)	0.024 (−0.152; 0.199)	**0.522 (0.396; 0.629)***	**0.195 (0.037; 0.343)***	**0.177 (0.010; 0.334)***	0.104 (−0.064; 0.267)	0.027 (−0.165; 0.217)	0.011 (−0.148; 0.170)	−0.078 (−0.234; 0.083)	−0.019 (−0.178; 0.140)
p-Se (µg/L)	0.088 (−0.072; 0.245)	−0.056 (−0.231; 0.123)	**0.413 (0.271; 0.537)***	0.129 (−0.032; 0.283)	**0.217 (0.051; 0.372)***	0.120 (−0.049; 0.283)	0.110 (−0.084; 0.297)	−0.110 (−0.265; 0.051)	**-0.160 (−0.312; 0.001)***	−0.119 (−0.274; 0.042)
Zn (mg/L)	0.133 (−0.027; 0.285)	−0.003 (−0.178; 0.173)	0.001 (−0.158; 0.161)	−0.059 (−0.216; 0.101)	**0.218 (0.053; 0.372)***	0.030 (−0.138; 0.196)	**0.212 (0.022; 0.388)***	−0.052 (−0.209; 0.108)	0.010 (−0.150; 0.169)	−0.121 (−0.275; 0.039)
Non-essential metals										
As (µg/L)	**0.202 (0.045; 0.350)***	−0.096 (−0.267; 0.082)	**0.475 (0.342; 0.590)***	**0.289 (0.136; 0.428)***	**0.260 (0.097; 0.409)***	0.151 (−0.017; 0.310)#	0.090 (−0.102; 0.276)	−0.031 (−0.189; 0.128)	−0.011 (−0.171; 0.148)	−0.018 (−0.177; 0.141)
Cd (µg/L)	−0.132 (−0.284; 0.028)	−0.138 (−0.306; 0.039)	**-0.208 (−0.355; −0.051)***	**-0.224 (−0.370; −0.068)***	**-0.191 (−0.347; −0.025)***	−0.152 (−0.311; 0.016)#	−0.018 (−0.208; 0.174)	**0.773 (0.700; 0.830)***	**0.731 (0.647; 0.798)***	**0.189 (0.030; 0.338)***
Hg (µg/L)	**0.170 (0.012; 0.320)***	0.048 (−0.129; 0.222)	**0.450 (0.313; 0.568)***	0.079 (−0.081; 0.235)	0.139 (−0.029; 0.299)	0.068 (−0.101; 0.232)	0.024 (−0.168; 0.213)	0.053 (−0.107; 0.210)	−0.005 (−0.165; 0.155)	0.066 (−0.094; 0.223)
Pb (µg/L)	0.140 (−0.019; 0.292)#	0.013 (−0.164; 0.188)	−0.009 (−0.168; 0.151)	0.066 (−0.094; 0.223)	**0.181 (0.014; 0.338)***	0.149 (−0.019; 0.308)#	0.093 (−0.100; 0.279)	−0.031 (−0.189; 0.128)	0.084 (−0.077; 0.240)	0.026 (−0.133; 0.185)
Principal components										
PC-1	**0.181 (0.022; 0.331)***	−0.041 (−0.216; 0.138)	**0.567 (0.448; 0.667)***	**0.204 (0.045; 0.353)***	**0.262 (0.098; 0.412)***	0.135 (−0.034; 0.297)	0.106 (−0.088; 0.293)	−0.029 (−0.188; 0.131)	−0.077 (−0.235; 0.084)	−0.063 (−0.221; 0.098)
PC-2	0.096 (−0.065; 0.252)	**0.197 (0.021; 0.362)***	−0.112 (−0.267; 0.049)#	**-0.163 (−0.350; −0.003)***	**0.217 (0.050; 0.371)***	−0.039 (−0.206; 0.130)	0.108 (−0.087; 0.294)	0.071 (−0.089; 0.228)	**0.190 (0.031; 0.341)***	−0.048 (−0.207; 0.113)

Spearman correlation coefficients (r_s) with 95% confidence interval (95% CI) for the correlation. Bold values and * indicate a significant correlation ($p < 0.050$), while # indicate a borderline significant correlation (p: ≥0.050 and 0.080). Some variables were categorical with the following categories: [a] Educational level (Primary School, High School, Technical college, and University), [b] Personal income/ [c] Household Income (<100.000, 100.000–250.000, and > 250.000 DKK/year), [d] Current alcohol intake (0 drinks/week, 1–7 drinks/week, and ≥ 8 drinks/week), [e] Smoking history (Never, Former, and Current). For personal income, household income, and alcohol intake the answer possibility "Don't know" was omitted in the analysis. The metals were measured in whole blood (WB), whereas selenium was also measured in plasma (P). WB-Se: Whole blood Selenium; p-Se: plasma Selenium; n: number of participants included in the analyses. PC: principal components; PC-1 strongly correlated with As, Hg and Se (whole blood and plasma): PC-2 strongly correlated with Ca, Cu, Fe, Mg, and Zn.

Table 4. Adjusted associations between metal concentrations and intake of traditional food groups (times per month).

	Marine mammals ($n = 110$) β (95%CI)	Seabirds ($n = 106$) β (95%CI)	Greenlandic Fish ($n = 142$) β (95%CI)	Shellfish ($n = 148$) β (95%CI)	Dried Fish ($n = 151$) β (95%CI)	Terrestrial animals ($n = 145$) β (95%CI)	Berries ($n = 141$) β (95%CI)	All traditional foods summed ($n = 97$) β (95%CI)
Essential metals								
Ca (mg/L)	0.005 (−0.011; 0.021)	0.003 (−0.020; 0.027)	−0.010 (−0.030; 0.009)	−0.004 (−0.019; 0.011)	0.001 (−0.012; 0.015)	−0.001 (−0.015; 0.014)	−0.008 (−0.021; 0.004)	−0.001 (−0.025; 0.023)
Cu (mg/L)	−0.002 (−0.052; 0.049)	0.008 (−0.053; 0.070)	0.005 (−0.048; 0.059)	0.012 (−0.028; 0.053)	−0.001 (−0.035; 0.034)	−0.014 (−0.056; 0.027)	0.017 (−0.018; 0.052)	−0.005 (−0.077; 0.068)
Fe (mg/L)	−0.012 (−0.029; 0.005)	−0.010 (−0.035; 0.014)	0.001 (−0.020; 0.022)	0.000 (−0.017; 0.017)	−0.013 (−0.028; 0.001)#	0.002 (−0.014; 0.018)	0.006 (−0.008; 0.020)	−0.022 (−0.046; 0.003)#
Mg (mg/L)	0.005 (−0.021; 0.030)	−0.016 (−0.053; 0.021)	−0.013 (−0.043; 0.016)	−0.001 (−0.024; 0.022)	−0.013 (−0.033; 0.008)	0.012 (−0.010; 0.034)	0.002 (−0.018; 0.021)	−0.009 (−0.045; 0.027)
Mn (µg/L)	−0.001 (−0.068; 0.066)	−0.014 (−0.111; 0.084)	−0.015 (−0.094; 0.063)	**−0.089 (−0.147; −0.032)***	0.005 (−0.050; 0.059)	−0.017 (−0.077; 0.044)	−0.026 (−0.077; 0.025)	−0.004 (−0.101; 0.094)
WB-Se (µg/L)	**0.078 (0.000; 0.155)***	**0.220 (0.091; 0.348)***	**0.111 (0.012; 0.209)***	0.048 (−0.041; 0.138)	**0.138 (0.062; 0.214)***	**0.117 (0.034; 0.200)***	0.062 (−0.013; 0.136)	**0.121 (0.018; 0.224)***
p-Se (µg/L)	0.031 (−0.001; 0.062)	**0.053 (0.007; 0.100)***	**0.051 (0.013; 0.089)***	**0.041 (0.011; 0.070)***	**0.033 (0.005; 0.060)**	0.024 (−0.006; 0.055)	0.022 (−0.003; 0.048)	0.032 (−0.010; 0.075)
Zn (mg/L)	−0.020 (−0.057; 0.016)	**−0.056 (−0.108; −0.004)***	−0.019 (−0.061; 0.022)	−0.004 (−0.037; 0.030)	**−0.030 (−0.059; 0.000)***	−0.005 (−0.039; 0.029)	0.014 (−0.013; 0.041)	**−0.052 (−0.103; −0.001)***
Non-essential metals								
As (µg/L)	**0.255 (0.097; 0.412)***	**0.315 (0.104; 0.527)***	**0.381 (0.216; 0.545)***	0.139 (−0.002; 0.281)#	**0.240 (0.112; 0.368)***	0.058 (−0.093; 0.209)	0.085 (−0.037; 0.207)	**0.309 (0.087; 0.530)***
Cd (µg/L)	−0.046 (−0.173; 0.081)	−0.135 (−0.337; 0.067)	0.052 (−0.104; 0.208)	0.092 (−0.033; 0.216)	−0.008 (−0.120; 0.103)	−0.006 (−0.124; 0.112)	−0.063 (−0.161; 0.036)	0.008 (−0.167; 0.183)
Hg (µg/L)	**0.430 (0.289; 0.572)***	**0.455 (0.222; 0.687)***	**0.323 (0.120; 0.527)***	0.137 (−0.027; 0.301)	**0.363 (0.230; 0.497)***	0.048 (−0.125; 0.220)	0.071 (−0.075; 0.218)	**0.415 (0.181; 0.649)***
Pb (µg/L)	−0.047 (−0.217; 0.123)	−0.015 (−0.257; 0.226)	0.125 (−0.050; 0.299)	0.046 (−0.098; 0.191)	−0.032 (−0.162; 0.098)	0.021 (−0.124; 0.167)	0.040 (−0.081; 0.162)	−0.031 (−0.264; 0.202)
Principal components								
PC-1	**0.025 (0.012; 0.038)***	**0.052 (0.025; 0.079)***	**0.036 (0.015; 0.057)***	**0.027 (0.008; 0.046)***	**0.037 (0.021; 0.054)***	0.015 (−0.002; 0.032)	0.016 (−0.001; 0.033)#	**0.026 (0.008; 0.044)***
PC-2	−0.009 (−0.025; 0.007)	−0.018 (−0.039; 0.003)	−0.008 (−0.026; 0.011)	−0.003 (−0.017; 0.012)	**−0.014 (−0.027; −0.002)***	0.004 (−0.010; 0.018)	0.005 (−0.007; 0.017)	−0.014 (−0.037; 0.008)

Linear regression analyses with metals as dependent variable and food intake (times per month) as independent variable with age, BMI, town, sex, education, house income, and smoking history as covariates. The analyses were performed with ln transformed variables. Unadjusted results are shown in Table S9. Bold values and * indicate a significant correlation ($p < 0.050$), while # indicate a borderline significant correlation (p: ≥0.050 and 0.080). The metals were measured in whole blood (WB), whereas selenium was also measured in plasma (P). WB-Se: Whole blood Selenium; p-Se: plasma Selenium; n: number of participants included in the analyses; β (95%CI): Beta coefficients from the linear regression analyses with 95% confidence interval. PC: principal components; PC-1 strongly correlated with As, Hg and Se (whole blood and plasma): PC-2 strongly correlated with Ca, Cu, Fe, Mg, and Zn.

Table 5. Adjusted associations between metal concentrations and intake of imported food groups (times per month).

	Meat products ($n = 157$) β (95%CI)	Carbohydrate foods ($n = 160$) β (95%CI)	Sauce ($n = 161$) β (95%CI)	Vegetables ($n = 160$) β (95%CI)	Fruit ($n = 157$) β (95%CI)	Fast food ($n = 154$) β (95%CI)	Sweets & Snacks ($n = 157$) β (95%CI)	All imported food groups summed ($n = 142$) β (95%CI)
Essential metals								
Ca (mg/L)	0.014 (−0.005; 0.033)	0.012 (−0.007; 0.031)	0.001 (−0.010; 0.013)	**−0.013 (−0.023; −0.002)***	−0.010 (−0.022; 0.002)	−0.005 (−0.020; 0.010)	−0.011 (−0.027; 0.005)	0.005 (−0.027; 0.036)
Cu (mg/L)	−0.014 (−0.069; 0.040)	−0.027 (−0.078; 0.025)	−0.014 (−0.045; 0.017)	−0.003 (−0.033; 0.027)	0.011 (−0.024; 0.046)	0.015 (−0.027; 0.057)	0.002 (−0.044; 0.048)	−0.042 (−0.135; 0.050)
Fe (mg/L)	0.000 (−0.021; 0.021)	−0.011 (−0.032; 0.010)	−0.001 (−0.013; 0.011)	0.007 (−0.004; 0.019)	0.005 (−0.008; 0.019)	−0.015 (−0.031; 0.002)	0.010 (−0.008; 0.028)	−0.007 (−0.042; 0.029)
Mg (mg/L)	0.005 (−0.025; 0.034)	−0.002 (−0.031; 0.028)	0.000 (−0.017; 0.017)	−0.003 (−0.019; 0.014)	0.002 (−0.017; 0.021)	−0.007 (−0.031; 0.017)	−0.004 (−0.029; 0.021)	−0.016 (−0.064; 0.033)
Mn (µg/L)	0.061 (−0.019; 0.141)	−0.009 (−0.088; 0.069)	−0.004 (−0.05; 0.043)	−0.033 (−0.078; 0.012)	**−0.064 (−0.114; −0.015)***	−0.019 (−0.080; 0.043)	**−0.098 (−0.161; −0.035)***	**−0.129 (−0.255; −0.003)***
WB-Se (µg/L)	−0.073 (−0.190; 0.044)	0.072 (−0.042; 0.187)	0.022 (−0.046; 0.090)	−0.021 (−0.086; 0.044)	0.004 (−0.072; 0.079)	−0.012 (−0.102; 0.078)	0.016 (−0.082; 0.114)	−0.044 (−0.238; 0.150)
p-Se (µg/L)	−0.018 (−0.059; 0.024)	0.015 (−0.026; 0.057)	0.021 (−0.003; 0.045)	0.017 (−0.005; 0.040)	**0.052 (0.027; 0.078)***	−0.001 (−0.035; 0.033)	**0.037 (0.003; 0.072)***	0.061 (−0.006; 0.127)[#]
Zn (mg/L)	0.026 (−0.018; 0.070)	−0.034 (−0.076; 0.009)	−0.015 (−0.041; 0.010)	**0.025 (0.001; 0.050)***	0.023 (−0.004; 0.051)	−0.011 (−0.046; 0.024)	0.005 (−0.032; 0.043)	−0.012 (−0.083; 0.058)
Non – essential metals								
As (µg/L)	−0.169 (−0.368; 0.030)	0.012 (−0.186; 0.210)	0.015 (−0.102; 0.132)	−0.056 (−0.168; 0.056)	−0.107 (−0.233; 0.018)	0.001 (−0.158; 0.160)	0.025 (−0.144; 0.194)	−0.180 (−0.507; 0.148)
Cd (µg/L)	−0.046 (−0.203; 0.111)	−0.016 (−0.175; 0.142)	0.015 (−0.079; 0.109)	−0.071 (−0.160; 0.018)	0.016 (−0.082; 0.113)	**0.155 (0.031; 0.279)***	0.084 (−0.050; 0.219)	0.079 (−0.161; 0.319)
Hg (µg/L)	**−0.434 (−0.655; −0.213)***	0.088 (−0.145; 0.321)	−0.032 (−0.169; 0.104)	0.059 (−0.070; 0.188)	0.040 (−0.112; 0.192)	−0.086 (−0.273; 0.102)	0.071 (−0.127; 0.269)	−0.272 (−0.650; 0.107)
Pb (µg/L)	0.051 (−0.144; 0.246)	−0.032 (−0.223; 0.160)	−0.105 (−0.215; 0.005)[#]	−0.090 (−0.197; 0.018)	−0.028 (−0.153; 0.097)	0.053 (−0.097; 0.203)	−0.028 (−0.190; 0.134)	−0.147 (−0.470; 0.176)
Principal components								
PC-1	−0.022 (−0.048; 0.004)	0.013 (−0.012; 0.038)	0.006 (−0.009; 0.021)	0.004 (−0.010; 0.019)	0.006 (−0.010; 0.023)	0.002 (−0.019; 0.022)	0.009 (−0.013; 0.031)	−0.003 (−0.046; 0.040)
PC-2	0.001 (−0.018; 0.019)	−0.010 (−0.028; 0.008)	−0.002 (−0.013; 0.009)	0.009 (−0.001; 0.020)[#]	0.011 (−0.000; 0.023)[#]	−0.007 (−0.022; 0.007)	0.003 (−0.013; 0.019)	−0.004 (−0.035; 0.026)

Linear regression analyses with metals were dependent variable and food intake (times per month) as independent variable with age, BMI, town, sex, education, house income, and smoking history as covariates. The analyses were performed with ln transformed variables. Unadjusted results are shown in Table S10. Bold values and * indicate a significant correlation ($p < 0.050$), while [#] indicate a borderline significant correlation (p: ≥0.050 and 0.080). The metals were measured in whole blood (WB), whereas selenium was also measured in plasma (P). WB-Se: Whole blood Selenium; p-Se: plasma Selenium; n: number of participants included in the analyses; β (95%CI): Beta coefficients from the linear regression analyses with 95% confidence interval. PC: principal components; PC-1 strongly correlated with As, Hg and Se (whole blood and plasma): PC-2 strongly correlated with Ca, Cu, Fe, Mg, and Zn.

Table 6. Percentage exceeding the international guidance values for mercury.

Guidance values	Target population	Fathers (n = 70)	Mothers (n = 92)	All (n = 162)
Health Canada				
Percentage above 8.0 µg/L Hg	Pregnant women Females ≤49 years Males ≤18 years	30.0%	21.7%	25.3%
Percentage above 20.0 µg/L Hg	Females ≥50 years Males >18 years	2.9%	3.3%	3.1%
German human biomonitoring Commission				
Percentage above 5.0 µg/L Hg (HBM I)[a]	General population	51.4%	40.2%	45.0%
Percentage above 15.0 µg/L Hg (HBM II)[a]	General population	4.3%	5.4%	4.9%

[a]Health based guidance values (HBM values) for mercury in blood derived by the German Human Biomonitoring Commission. The HBM I and HBM II is defined by Apel et al., 2017: "The HBM I value represents the concentration of a substance in human biological material at which and below which, according to the current knowledge and assessment by the HBM Commission, there is no risk of adverse health effects, and, consequently, no need for action. The HBM II value describes the concentration of a substance in human biological material at which and above which adverse health effects are possible and, consequently, an acute need for the reduction of exposure and the provision of biomedical advice is given".

giving birth (Table 7), as well as intra-individual differences between the two timepoints for all metals (Table 2). Some of the changes may not only be due to temporal trends of the metals in human blood, but could also be influenced by changes in food intake, changes in lifestyle and socio-economic status (household income, smoking, etc.), physiological changes during pregnancy, and natural effects of ageing [66]. Most of the metals have relatively short half-lives of hours to months in the whole body or blood [4,67–72], and thus, they are more influenced by seasonal differences in food intake than compounds with longer half-lives. Only Cd has a half-live of several years [73]. We did, however, see positive correlations between the individual concentrations at inclusion and follow-up (Table 2), indicating that for many of the metals the relative ranking within the study is stable even though significant changes have been found in the absolute concentrations (Table 2). When the analyses were restricted to women with blood samples taken in the same season at inclusion and follow-up (results not shown), the Pearson correlations were stronger for some metals (Fe, Zn, As, and Pb) and similar to the total population for the others (Mg, Mn, WB-Se, p-Se, Cd, and Hg), indicating that some seasonal influence may be present for some metals. Furthermore, during pregnancy, the development of the uterus and foetus requires major physiological changes, including expansion of the volumes of blood, plasma and erythrocytes, enhanced metabolism, and increased renal perfusion [66]. Even though not fully explored yet, studies have also reported changes in both essential and non-essential metals during pregnancy [74]. At the establishment of the ACCEPT cohort, the blood samples were taken during the 1st trimester where the physiological changes are less pronounced than later in pregnancy; however, we cannot fully ensure that the metal concentrations did not change during the first trimester of pregnancy, and therefore the results must be assessed with some caution. The changes in Se and Cd concentrations seen from inclusion in the ACCEPT cohort [19] to the present follow-up is generally consistent with time trends seen in other Arctic studies [75–77]. The increases in Hg and Pb from inclusion in the ACCEPT cohort [19] to the present follow-up are, however, less consistent with other Arctic studies, in which a decrease and stable trend was generally observed [63,65,75,77]. However, the disparities may be explained by the different study designs, time periods, and populations.

Correlation between metals

Several of the metal concentrations correlated significantly (Figure S2). The majority correlated positively, whereas Ca and Cu generally correlated inversely with other metals. Both similar exposure sources and interactions in the absorbance, metabolism, and excretion of the metals can affect the correlations. The interaction between Ca and Pb is often studied, and the studies have shown that high Ca intake decreases the Pb absorption by occupying the gastro-intestinal transporter and low Ca acts as an inhibitor for the Pb bone release and thereby increasing the total body Pb burden [78–82]. Some studies found that Ca intake (consumption of milk/dairy products or Ca supplementation) were inversely related to blood Pb concentrations [83–85], supporting the inverse correlation between Ca and Pb found in the present study. Similar interactions have been reported for Ca with Fe, Mg, and Zn [86–90], in accordance with the (borderline) significant inverse correlations observed in the present study. The borderline significant inverse correlation between Ca and Mg may be of importance for human health, as increasing evidence suggest that a high Ca/Mg ratio increases the risk of cardiovascular disease, metabolic syndrome, some cancers, and total mortality [91]. Ca only correlated positively with Cu, which may be explained by the low faecal loss and improved body retention of Cu with high Ca intake, as suggested by

Table 7. Comparison of the metal concentrations in the present study with other Arctic studies with samples collected after 2010.

Reference	Region, Country	Sampling time	Population	Age range (years)	Concentration Men	Concentration Women	Comparison with present study (percentage of the concentration in the present study) ↔
Whole blood Ca							
Present study	*West and Disko Bay, Greenland*	2019-2020	Men and women	*24-55*	*55.8 mg/L[b]*	61.0 mg/L[b]	
[19] Bank-Nielsen et al., 2019 [e]	All regions, Greenland	2010-2015	Pregnant (n=344)	18-43		63.9 mg/L[b]	↔ : 105% of present study
[19] Bank-Nielsen et al., 2019 [e]	West, Greenland	2010-2015	Pregnant (n=198)	18-42		63.8 mg/L[b]	↔ : 105% of present study
[19] Bank-Nielsen et al., 2019 [e]	Disko Bay, Greenland	2010-2015	Pregnant (n=93)	18-41		64.3 mg/L[b]	↔ : 105% of present study
Whole blood Fe							
Present study	*West and Disko Bay, Greenland*	*2019-2020*	*Men and women*	*24-55*	*513 mg/L[b]*	*451 mg/L[b]*	
[19] Bank-Nielsen et al., 2019 [e]	All regions, Greenland	2010-2015	Pregnant (n=502)	18-43		437 mg/L[b]	↔ : 97% of present study
[19] Bank-Nielsen et al., 2019 [e]	West, Greenland	2010-2015	Pregnant (n=285)	18-42		440 mg/L[b]	↔ : 98% of present study
[19] Bank-Nielsen et al., 2019 [e]	Disko Bay, Greenland	2010-2015	Pregnant (n=121)	18-41		431 mg/L[b]	↔ : 96% of present study
[32] Long et al., 2023	East coast, Greenland	2013-2015	Men (n=36) and women (n=21)	18-61	462 mg/kg [b, f]	432 mg/kg [b, f]	↔ : 90-96% of present study
Whole blood Mg							
Present study	*West and Disko Bay, Greenland*	*2019-2020*	*Men and women*	*24-55*	*42.5 mg/L[b]*	*40.3 mg/L[b]*	
[19] Bank-Nielsen et al., 2019 [e]	All regions, Greenland	2010-2015	Pregnant (n=344)	18-43		37.6 mg/L[b]	↔ : 93% of present study
[19] Bank-Nielsen et al., 2019 [e]	West, Greenland	2010-2015	Pregnant (n=198)	18-42		38.0 mg/L[b]	↔ : 94% of present study
[19] Bank-Nielsen et al., 2019 [e]	Disko Bay, Greenland	2010-2015	Pregnant (n=93)	18-41		36.7 mg/L[b]	↔ : 91% of present study
Whole blood Cu							
Present study	*West and Disko Bay, Greenland*	*2019-2020*	*Men and women*	*24-55*	*0.828 mg/L[b]*	*0.952 mg/L[b]*	
[19] Bank-Nielsen et al., 2019 [e]	All regions, Greenland	2010-2015	Pregnant (n=488)	18-43		1.4 mg/L[b]	↑ : 147% of present study
[19] Bank-Nielsen et al., 2019 [e]	West, Greenland	2010-2015	Pregnant (n=284)	18-42		1.4 mg/L[b]	↑ : 147% of present study
[19] Bank-Nielsen et al., 2019 [e]	Disko Bay, Greenland	2010-2015	Pregnant (n=121)	18-41		1.4 mg/L[b]	↑ : 147% of present study
[57] Dudarev et al., 2016	Murmansk Oblast, Russia	2013	Men (n=18) and women (n=32)	26-65	1.226 mg/L[a]	1.436 mg/L[a]	↑ : 148-150% of present study
[58] Ratelle et al., 2020	Northwest Territories, Canada	2016-2017	Pooled men+women (n=276)	18-88	0.980 mg/L[a]		↔ / ↑ : 102-118% of present study
[59] Sobolev et al., 2021	Nenets Autonomous Okurg, Russia	2018	Men (n=93) and women (n=204)	18-87	1.01 mg/L[c]	1.14 mg/L[c]	↑ : 121% of present study
[60] Drysdale et al., 2021	Yukon, Canada	2019	Pooled men+women (n=54)	20-75	0.970 mg/L[a]		↔ / ↑ : 102-117% of present study
Whole blood Mn							
Present study	*West and Disko Bay, Greenland*	*2019-2020*	*Men and women*	*24-55*	*8.61 µg/L[b]*	*9.93 µg/L[b]*	
[19] Bank-Nielsen et al., 2019 [e]	All regions, Greenland	2010-2015	Pregnant (n=502)	18-43		16.0 µg/L[b]	↑ : 161% of present study
[19] Bank-Nielsen et al., 2019 [e]	West, Greenland	2010-2015	Pregnant (n=285)	18-42		15.7 µg/L[b]	↑ : 158% of present study
[19] Bank-Nielsen et al., 2019 [e]	Disko Bay, Greenland	2010-2015	Pregnant (n=121)	18-41		17.7 µg/L[b]	↑ : 178% of present study
[32] Long et al., 2023	East coast, Greenland	2013-2015	Men (n=36) and women (n=21)	18-61	11.1 µg/kg [b, f]	15.0 µg/kg [b, f]	↑ : 129-151% of present study
[57] Dudarev et al., 2016	Murmansk Oblast, Russia	2013	Men (n=18) and women (n=32)	26-65	46.0 µg/L[a]	53.2 µg/L[a]	↑ : 535% of present study
[58] Ratelle et al., 2020	Northwest Territories, Canada	2016-2017	Pooled men+women (n=276)	18-88	10 µg/L[a]		↔ / ↑: 101-116% of present study
[59] Sobolev et al., 2021	Nenets Autonomous Okurg, Russia	2018	Men (n=93) and women (n=204)	18-87	13.2 µg/L[c]	14.0 µg/L[c]	↑ : 141-153% of present study
[60] Drysdale et al., 2021	Yukon, Canada	2019	Pooled men+women (n=54)	20-75	12 µg/L[a]		↑ : 121-139% of present study
Whole blood Zn							
Present study	*West and Disko Bay, Greenland*	*2019-2020*	*Men and women*	*24-55*	*6.01 mg/L[b]*	*5.42 mg/L[b]*	
[19] Bank-Nielsen et al., 2019 [e]	All regions, Greenland	2010-2015	Pregnant (n=502)	18-43		4.6 mg/L[b]	↓ : 85% of present study
[19] Bank-Nielsen et al., 2019 [e]	West, Greenland	2010-2015	Pregnant (n=285)	18-42		4.7 mg/L[b]	↓ : 87 % of present study
[19] Bank-Nielsen et al., 2019 [e]	Disko Bay, Greenland	2010-2015	Pregnant (n=121)	18-41		4.4 mg/L[b]	↓ : 81% of present study
[32] Long et al., 2023	East coast, Greenland	2013-2015	Men (n=36) and women (n=21)	18-61	5.16 mg/kg [b, f]	4.77 mg/kg [b, f]	↓ : 87 % of present study
[57] Dudarev et al., 2016	Murmansk Oblast, Russia	2013	Men (n=18) and women (n=32)	26-65	8.10 mg/L[a]	7.66 mg/L[a]	↑ : 135-141% of present study
[58] Ratelle et al., 2020	Northwest Territories, Canada	2016-2017	Pooled men+women (n=276)	18-88	5.60 mg/L[a]		↔ : 93-103% of present study
[59] Sobolev et al., 2021	Nenets Autonomous Okurg, Russia	2018	Men (n=93) and women (n=204)	18-87	9.4 mg/L[c]	8.6 mg/L[c]	↑ : 158% of present study
[60] Drysdale et al., 2021	Yukon, Canada	2019	Pooled men+women (n=54)	20-75	5.70 mg/L[a]		↔ : 94-105% of present study
Whole blood Se							
Present study	*West and Disko Bay, Greenland*	*2019-2020*	*Men and women*	*24-55*	*196 µg/L[b]*	*201 µg/L[b]*	
[26] AMAP, 2016, Berner[d]	Alaska, US	2009-2012	Pregnant (n=160)	Mean: 26.5		181 µg/L[a]	↔ : 90% of present study
[19] Bank-Nielsen et al., 2019 [e]	All regions, Greenland	2010-2015	Pregnant (n=502)	18-43		121 µg/L[b]	↓ : 60% of present study
[19] Bank-Nielsen et al., 2019 [e]	West, Greenland	2010-2015	Pregnant (n=285)	18-42		116 µg/L[b]	↓ : 58% of present study
[19] Bank-Nielsen et al., 2019 [e]	Disko Bay, Greenland	2010-2015	Pregnant (n=121)	18-41		125 µg/L[b]	↓ : 62% of present study
[26] AMAP, 2016, Dewailly/Ayotte[d]	Nunavik, Canada	2012-2013	Pregnant (n=206)	18-41		300-320 µg/L[a]	↑ : 149-159% of present study
[61] Rylander et al., 2011	Izihma, Komi Republic, Russia	2009-2010	Men (n=25) and women (n=25)	15-55	88 µg/L[a]	87 µg/L[a]	↓ : 44% of present study
[61] Rylander et al., 2011	Usinsk, Komi Republic, Russia	2009-2010	Men (n=25) and women (n=25)	19-62	99 µg/L[a]	100 µg/L[a]	↓ : 50% of present study

(*Continued*)

Table 7. (Continued).

[32] Long et al., 2023	East coast, Greenland	2013-2015	Men (n=36) and women (n=21)	18-61	210 µg/kg [b]	340 µg/kg [b]	↔ / ↑: 107-169% of present study
[58] Ratelle et al., 2020	Northwest Territories, Canada	2016-2017	Men and women (n=276)	18-88	170 µg/L[a]	170 µg/L[a]	↓ : 85% of present study
[31] AMAP, 2021: Lemire/Blanchette[d]	Nunavik	2017	Men (n=407) and women (n=791)	18-86	280 µg/L[a]	330 µg/L[a]	↑ : 143-164% of present study
[59] Sobolev et al., 2021	Nenets Autonomous Okurg, Russia	2018	Men (n=93) and women (n=204)	18-87	124 µg/L[a]	125 µg/L[a]	↓ : 63% of present study
[60] Drysdale et al., 2021	Yukon, Canada	2019	Pooled men+women (n=54)	20-75	170 µg/L[a]		↓ : 85% of present study
Serum/Plasma Se							
Present study	***West and Disko Bay, Greenland***	***2019-2020***	***Men and women***	***24-55***	***94.7 µg/L[b]***	***91.1 µg/L[b]***	
[19] Bank-Nielsen et al., 2019 [e]	All regions, Greenland	2010-2015	Pregnant (n=502)	18-43		75.8 µg/L[b]	↓ : 83% of present study
[19] Bank-Nielsen et al., 2019 [e]	West, Greenland	2010-2015	Pregnant (n=285)	18-42		75.9 µg/L[b]	↓ : 83% of present study
[19] Bank-Nielsen et al., 2019 [e]	Disko Bay, Greenland	2010-2015	Pregnant (n=122)	18-41		70.9 µg/L[b]	↓ : 78% of present study
[32] Long et al., 2023	East coast, Greenland	2013-2015	Men (n=36) and women (n=21)	18-61	89 µg/kg [b, f]	105 µg/kg [b, f]	↔ / ↑: 93-115% of present study
[62] Laustsen et al., 2021	West and Disko Bay, Greenland	2016-2017	Seafood processing worker, pooled men+women (n=324)	16-68	96.22 µg/L[c]		↔ : 104% of present study
Whole blood As							
Present study	***West and Disko Bay, Greenland***	***2019-2020***	***Men and women***	***24-55***	***6.51 µg/L[b]***	***7.27 µg/L[b]***	
[19] Bank-Nielsen et al., 2019 [e]	All regions, Greenland	2010-2015	Pregnant (n=502)	18-43		4.2 µg/L[b]	↓ : 58% of present study
[19] Bank-Nielsen et al., 2019 [e]	West, Greenland	2010-2015	Pregnant (n=285)	18-42		4.2 µg/L[b]	↓ : 58% of present study
[19] Bank-Nielsen et al., 2019 [e]	Disko Bay, Greenland	2010-2015	Pregnant (n=121)	18-41		5.5 µg/L[b]	↓ : 76% of present study
[57] Dudarev et al., 2016	Murmansk Oblast, Russia	2013	Men (n=18) and women (n=32)	26-65	4.43 µg/L[a]	5.19 µg/L[a]	↓ : 68% of present study
[32] Long et al., 2023	East coast, Greenland	2013-2015	Men (n=36) and women (n=21)	18-61	7.0 µg/kg [b, f]	11 µg/kg [b, f]	↔ / ↑: 108-151% of present study
[59] Sobolev et al., 2021	Nenets Autonomous Okurg, Russia	2018	Men (n=93) and women (n=204)	18-87	3.9 µg/L[a]	5.2 µg/L[a]	↓ : 60-72% of present study
[60] Drysdale et al., 2021	Yukon, Canada	2019	Pooled men+women (n=54)	20-75	0.54 µg/L[a]		↓ : 7.9% of present study
Whole blood Cd							
Present study	***West and Disko Bay, Greenland***	***2019-2020***	***Men and women***	***24-55***	***0.39 µg/L[b]***	***0.46 µg/L[b]***	
[26] AMAP, 2016, Berner[d]	Alaska, US	2009-2012	Pregnant (n=160)	Mean: 26.5		0.2 µg/L[a]	↓ : 44% of present study
[19] Bank-Nielsen et al., 2019 [e]	All regions, Greenland	2010-2015	Pregnant (n=502)	18-43		1.5 µg/L[b]	↑ : 326% of present study
[19] Bank-Nielsen et al., 2019 [e]	West, Greenland	2010-2015	Pregnant (n=285)	18-42		1.3 µg/L[b]	↑ : 283% of present study
[19] Bank-Nielsen et al., 2019 [e]	Disko Bay, Greenland	2010-2015	Pregnant (n=121)	18-41		1.4 µg/L[b]	↑ : 304% of present study
[63] Wennberg et al., 2017	Northern, Sweden	2004-2014	Men (n=152) and women (n=325)	25-35	0.12 µg/L[a]	0.16 µg/L[a]	↓ : 33% of present study
[61] Rylander et al., 2011	Izihma, Komi Republic, Russia	2009-2010	Men (n=25) and women (n=25)	15-55	0.43 µg/L[a]	0.40 µg/L[a]	↔ / ↓ : 87-110% of present study
[61] Rylander et al., 2011	Usinsk, Komi Republic, Russia	2009-2010	Men (n=25) and women (n=25)	19-62	0.28 µg/L[a]	0.23 µg/L[a]	↓ : 20-72% of present study
[57] Dudarev et al., 2016	Murmansk Oblast, Russia	2013	Men (n=18) and women (n=32)	26-65	0.97 µg/L[a]	0.59 µg/L[a]	↑ : 128-249% of present study
[32] Long et al., 2023	East coast, Greenland	2013-2015	Men (n=36) and women (n=21)	18-61	1.4 µg/kg [b, f]	1.4 µg/kg [b, f]	↑ : 304-359% of present study
[59] Sobolev et al., 2021	Nenets Autonomous Okurg, Russia	2018	Men (n=93) and women (n=204)	18-87	0.37 µg/L[a]	0.32 µg/L[a]	↔ / ↓ : 70-95% of present study
[58] Ratelle et al., 2020	Northwest Territories, Canada	2016-2017	Men and women (n=276)	18-88	0.37 µg/L[a]	0.40 µg/L[a]	↔ / ↓ : 87-95% of present study
[31] AMAP, 2021: Lemire/Blanchette[d]	Nunavik, Canada	2017	Men (n=407) and women (n=791)	18-86	1.6 µg/L[a]	1.7 µg/L[a]	↑ : 370-410% of present study
[60] Drysdale et al., 2021	Yukon, Canada	2019	Pooled men+women (n=54)	20-75	0.85 µg/L[a]		↑ : 185-218% of present study
Whole blood Hg							
Present study	***West and Disko Bay, Greenland***	***2019-2020***	***Men and women***	***24-55***	***5.11 µg/L[b]***	***4.24 µg/L[b]***	
[64] Mosites et al., 2020	Alaska, US	2009-2012	Pregnant (n=152)	Mean: 26.5		2.36 µg/L[b]	↓ : 56% of present study
[19] Bank-Nielsen et al., 2019 [e]	All regions, Greenland	2010-2015	Pregnant (n=502)	18-43		4.2 µg/L[b]	↔ : 100% of present study
[19] Bank-Nielsen et al., 2019 [e]	West, Greenland	2010-2015	Pregnant (n=285)	18-42		3.2 µg/L[b]	↓ :76% of present study
[19] Bank-Nielsen et al., 2019 [e]	Disko Bay, Greenland	2010-2015	Pregnant (n=121)	18-41		4.2 µg/L[b]	↔ : 100% of present study
[65] Adlard et al., 2021	Nunavik, Canada	2012-2013	Pregnant (n=95)	18-41		5.88 µg/L[b]	↑ : 139% of present study
[57] Dudarev et al., 2016	Murmansk Oblast, Russia	2013-2014	Pregnant (n=50)	20-42		0.95 µg/L[a]	↓ : 22% of present study
[65] Adlard et al., 2021	Iceland	2014-2015	Pregnant (n=50)	22-43		1.38 µg/L[b]	↓ : 33% of present study
[65] Adlard et al., 2021	Northern Norway	2014-2015	Pregnant (n=50)	21-40		1.20 µg/L[a]	↓ : 28% of present study
[65] Adlard et al., 2021	Northern Finland	2014	Pregnant (n=25)	21-39		0.93 µg/L[a]	↓ : 22% of present study
[65] Adlard et al., 2021	Northern, Sweden	2015-2016	Pregnant (n=51)	20-42		0.39 µg/L[a]	↓ : 9% of present study
[61] Rylander et al., 2011	Izihma, Komi Republic, Russia	2009-2010	Men (n=25) and women (n=25)	15-55	2.3 µg/L[a]	2.3 µg/L[a]	↓ : 45-54% of present study
[61] Rylander et al., 2011	Usinsk, Komi Republic, Russia	2009-2010	Men (n=25) and women (n=25)	19-62	2.2 µg/L[a]	2.3 µg/L[a]	↓ : 43-54% of present study
[57] Dudarev et al., 2016	Murmansk Oblast, Russia	2013	Men (n=18) and women (n=32)	26-65	3.08 µg/L[c]	2.18 µg/L[c]	↓ : 51-60% of present study
[32] Long et al., 2023	East coast, Greenland	2013-2015	Men (n=36) and women (n=21)	18-61	28 µg/kg [b, f]	21 µg/kg [b, f]	↑ : 495-548% of present study
[59] Sobolev et al., 2021	Nenets Autonomous Okurg, Russia	2018	Men (n=93) and women (n=204)	18-87	5.4 µg/L[a]	5.1 µg/L[a]	↔ / ↑ : 106-120% of present study

(*Continued*)

Table 7. (Continued).

[31] AMAP, 2021: Lemire/Blanchette[d]	Nunavik, Canada	2017	Men (n=407) and women (n=791)	18-86	8.1 μg/L[a]	10 μg/L[a]	↑ : 159-236% of present study
[60] Drysdale et al., 2021	Yukon, Canada	2019	Pooled men+women (n=54)	20-75	0.76 μg/L[a]		↓ : 18% of present study
Whole blood Pb							
Present study	***West and Disko Bay, Greenland***	***2019-2020***	***Men and women***	***24-55***	***12.8 μg/L[b]***	***7.79 μg/L[b]***	
[26] AMAP, 2016, Berner[d]	Alaska, US	2009-2012	Pregnant (n=160)	Mean: 26.5		7.4 μg/L[a]	↔ : 95% op present study
[19] Bank-Nielsen et al., 2019 [e]	All regions, Greenland	2010-2015	Pregnant (n=502)	18-43		6.3 μg/L[b]	↓ : 81% of present study
[19] Bank-Nielsen et al., 2019 [e]	West, Greenland	2010-2015	Pregnant (n=285)	18-42		6.7 μg/L[b]	↓ : 86% of present study
[19] Bank-Nielsen et al., 2019 [e]	Disko Bay, Greenland	2010-2015	Pregnant (n=121)	18-41		5.3 μg/L[b]	↓ :68% of present study
[26] AMAP, 2016, Dewailly/Ayotte[d]	Nunavik, Canada	2012-2013	Pregnant (n=206)	18-41		13-14 μg/L[a]	↑ : 167-180% of present study
[63] Wennberg et al., 2017	Northern, Sweden	2004-2014	Men (n=152) and women (n=325)	25-35	11.0 μg/L[a]	9.65 μg/L[a]	↓ : 86-124% of present study
[61] Rylander et al., 2011	Izihma, Komi Republic, Russia	2009-2010	Men (n=25) and women (n=25)	15-55	33 μg/L[a]	27 μg/L[a]	↑ : 258-347% of present study
[61] Rylander et al., 2011	Usinsk, Komi Republic, Russia	2009-2010	Men (n=25) and women (n=25)	19-62	32 μg/L[a]	23 μg/L[a]	↑ : 250-295% of present study
[57] Dudarev et al., 2016	Murmansk Oblast, Russia	2013	Men (n=18) and women (n=32)	26-65	23.06 μg/L[a]	14.39 μg/L[a]	↑ : 182% of present study
[32] Long et al., 2023	East coast, Greenland	2013-2015	Men (n=36) and women (n=21)	18-61	20 μg/kg [b, f]	15 μg/kg [b, f]	↑ : 156-193% of present study
[59] Sobolev et al., 2021	Nenets Autonomous Okurg, Russia	2018	Men (n=93) and women (n=204)	18-87	34.8 μg/L[a]	20.6 μg/L[a]	↑ : 264-272% of present study
[58] Ratelle et al., 2020	Northwest Territories, Canada	2016-2017	Men and women (n=276)	18-88	21.0 μg/L[a]	14.8 μg/L[a]	↑ : 164-190% of present study
[31] AMAP, 2021: Lemire/Blanchette[d]	Nunavik, Canada	2017	Men (n=407) and women (n=791)	18-86	28 μg/L[a]	24 μg/L[a]	↑ : 219-308% of present study
[60] Drysdale et al., 2021	Yukon, Canada	2019	Pooled men+women (n=54)	20-75	24 μg/L[a]		↑ : 188-308% of present study

The comparison of concentrations in the studies were calculated by as percentage of the present study by dividing the median levels and multiple with 100. A ↔ is given for concentrations within 90–110% of the present study, ↑ is given for concentrations > 110% of the present study, ↓ is given for concentrations < 90% of the present study. Green indicates concentration measured in the general population, yellow indicates concentrations measured in pregnant women. [a]Geometric mean; [b]Median; [c]Arithmetic mean; [d]Personal comment to the AMAP report authors; [e]The article presents metal concentrations of the pregnant ACCEPT women, and some of these women are followed up in the present study; [f] The unit for this study is in mg/kg or μg/kg – and not mg/L or μg/L as all other studies, however the results should be fairly comparable as the density of whole blood is 1.06 kg/L

Kies et al. [92]. It is well known that Cu interacts with Fe and Zn, but the relation is complex, and the mechanisms are not fully understood. The absorption of metals is partly dependent on the same divalent metal transporter-1 (DMT1). Fe can disturb Cu homoeostasis by altering the absorption and tissue distribution, and Cu depletion may be caused by high Fe intake [93–95], being in accordance with the inverse correlations of Cu with Fe and Zn found in the present study. As expected, Se correlated positively with the non-essential metals As and Hg, as they are all found in marine mammals and fish [23–25]. The correlation is relevant and important for human health, as Se counteracts and reduces the toxicity of heavy metals such as As, Cd, and Hg [96,97].

Determinants for metals

To explore the exposure sources, we investigated possible determinants for the metal concentrations (Figures 1–2, Table 3). Fe, Mg, Zn, Pb, and PC-2 (strongly correlated with Ca, Cu, Fe, Mg, and Zn) were lower in mothers than in fathers, while Ca, Cu, Mn, Se, and As were highest in mothers, which generally complies with previous findings in other populations [98–103].

We found a positive correlation between age and As, Hg, Pb (borderline) and PC-1 (strongly correlated with As, Hg, and Se). Other studies have also reported that concentrations of both the essential metals (Ca, Cu, Mg, Mn, and Zn) and non-essential metals (As, Cd, Hg, and Pb) differed between age groups in non-Arctic adults with highest concentration in the oldest age groups [19, 101, 102]. We had a narrow age-range from 24 to 55 years with 60% of the study population being between 30 and 40 years, which could explain why no significant correlation was seen for the non-essential metals. In support of our results, Bocca et al. did not find any differences in Cu, Mn, Zn, and Se between three age groups (18–40, 41–60, and >60 years) in a Italian population [104].

The influence of Ca on obesity have been debated [105]. Most research suggest that inadequate/low Ca intake and dairy consumption may affect BMI and obesity [106–112], in line with the inverse correlation between blood Ca and BMI found in the present study. The observed significantly inverse correlation of Zn and BMI in fathers in the stratified analyses was also in accordance with the literature [113].

Similar with the pregnant women at inclusion in the ACCEPT cohort [19], several metals correlated significantly with the *n*-3/*n*-6 FA ratio in the follow-up. At inclusion during pregnancy, Se, Hg, and Pb correlated positively with *n*-3/*n*-6 FA ratio [19]. In the present study, positive correlations of *n*-3/*n*-6 FA ratio with Se, As, and Hg were seen. The Mg concentration correlated inversely with n-3/n-6 FA ratio even though Mg did not associate significantly with any food intake. A study in rodents has previously found that n-3 FA affected the metabolism and excretion of Mg [114], which might explain the observed inverse correlation.

Most metals correlated with the socioeconomic factors (education or income) either positively or inversely, which may be explained by the previously reported significant correlations between socioeconomic factors and food intake among the study population [36].

Similar to Bocca et al. [104], we found that Mn and Zn correlated inversely and positively with alcohol intake, respectively. Alcohol intake may affect the blood Mn concentration by enhancing the Mn excretion and increase transport of Mn from the blood to other tissues [115]. The positive correlation of Zn and alcohol intake is also supported by Zn found in alcoholic beverages, due to absorption from soil by plants or release from the metallic containers [116].

Two metals, Mg and Cd, correlated positively with smoking. The positive correlation for Mg (pooled and mothers alone) was unexpected, as other studies found that smokers had a lower intake of Mg than non-smokers [117,118], and serum Mg level was found to be similar in smokers and non-smokers or higher in non-smokers [119,120]. We cannot fully explain the positive correlation seen in the present study. On the other side, the correlation between Cd and smoking is well-known [19,28,47]. Similar positive correlation was also seen at inclusion of the pregnant women [19,47]. In men and women from Nunavik, Cd was also associated with smoking, while consumption of caribou was only a minor exposure source in non-smokers [121]

Food intake and metal concentrations

Oral intake and ingestion through food and beverages are the major exposure source for all essential and non-essential metals included in the present study, except for Cd where tobacco smoking is the main exposure source in smokers. Significant associations between food intake and metal concentrations can be explained by the food items containing the metal, biological interactions between the metals, or confounding by intake of other food items or other non-dietary factors. The positive associations are often due to the food containing the metal of interest, whereas the inverse association can be more challenging to interpret.

Most of the significant associations between metal concentrations and food intake found in the present study were expected, such as the positive association between marine mammal intake and Se, As, and Hg [23, 25].

As expected, Se (whole blood and/or plasma) was positively associated with most traditional Greenlandic food groups. In previous Greenlandic studies, marine mammals, seabird, and fish was identified as main contributes to the Se intake [23,122]. Johansen et al. found, based on Greenlandic data from 1995 to 1996, that intake of marine mammals contributed with 52–62% of the Se intake, seabirds with 14–32%, fish with 16–23%, and terrestrial animals with less than 2% [23]. In the present study, we also found a positively significant association between intake of terrestrial animals and WB-Se concentration, even though the study by Johansen et al. found that terrestrial animals only contribute with less than 2% of the Se intake. However, the intake of terrestrial animals has increased over the last 25 years, since data from Johansen et al. was collected [23]. In the Population Health survey of Greenland, the proportion eating caribou at least once a week increased from 11% in 1993 to 21% in 2005–2007 [123], and in the present study 39% eat terrestrial animals at least once a week [36]. The plasma Se concentration also associated positively with the intake of the imported food groups (sauce, fruit, sweets & snacks), and the sum of all imported food groups. In the European population, sauce, fruit, and sweets & snacks are contributing to about 0.4–1.8%, 0.5–4% and 6% of the total Se intake, respectively [124,125]. The contribution to Se intake from sauce, fruit, and sweets & snacks in Greenland have not previously been reported. Here, we found a significant association even though the intake from these food groups may only contribute with few percentages to the total Se intake.

Mn was associated inversely with intake of shellfish, terrestrial animals (borderline), fruit, and sweets & snacks. These inverse associations were unexpected as crustaceans and molluscs, such as shellfish, cereal products, pulses, fruits, nuts, and chocolate are rich sources of Mn [126]. Main contributors to the Mn intake of European adults are cereal-based products, vegetables, and fruits [126]. The inverse association may be explained by residual confounding of socioeconomic status, even though we had adjusted for education and income. We have previously reported that education and income correlated positively with intake of shellfish, vegetables, fruits, and sweets & snacks [36]. Specific information on contributors to Mn intake in the Arctic population is not available and needs further studies.

Strengths and limitations of the study

One of the main strengths of our study is the inclusion of both men and women and the repeated intra-individual measurements in the mothers providing longitudinal metal data not previously reported for Greenland. We believe that the presented results reflect a large part of the general adult population in Greenland. However, metal concentrations might be different in other age groups and for participants from settlements at the north and east coast of Greenland (as previously discussed for persistent organic pollutants in [37]).

Another strength is the measurement of 11 different metals, including both essential and non-essential metals, in the same individuals. Other biomonitoring studies are often only focusing on Hg or few heavy metals, not revealing the full exposure pattern for the metals. As shown in our results, some of the metals are correlated and may have similar exposure source, which is important to consider before recommendations are given to the public about food choices to limit intake of non-essential heavy metals with negative health effects.

The metals can be measured in several matrices such as whole blood, serum, plasma, urine, hair, and nails, which have different advantages and disadvantages [127]. We measured all metals in whole blood (and Se in plasma as well); however, most other studies have measured Ca and Mg in serum which have been suggested as the optimal matrix for measurement of these metals. Even though whole blood can be used as a matrix for Ca and Mg measurement [128], the different matrices have made it impossible to compare our results with older Greenlandic studies using serum as a matrix [129–131]. Furthermore, some studies have found that Fe status may influence concentrations of some other metals (e.g. Cu, Mn, Zn, Pb, and Cd) [132,133]. As we did not measure serum ferritin, we are not able to conclude if some of the associations seen in the present study were mediated through the Fe status.

We collected information on food intake using FFQ, which contained many both traditional and imported food items. It is an important advance of the study that we can explore the association between the metal blood concentrations and food intake. The inclusion of both traditional and imported food items become more and more important with the changing dietary habits where the proportion of traditional and imported food was 14 and 86%, respectively, in the present study. However, the FFQ have some limitations. As the information on food intake were self-reported, recall bias might affect the dietary data accuracy. However, we believe that the possible recall would be non-differential and not affected by the individual's metal concentrations, therefore, reducing the magnitude of the associations found. We did not include information on cooking methods in our study; however, processing and cooking can influence the metal concentration in some food items. Rasmussen et al. reported that the concentrations of As, Zn, Se, Cd, Cu, and Fe were highest in raw unpeeled prawns, intermediate in cooked unpeeled prawns, and lowest in raw peeled prawns, except for Hg, which was highest in raw peeled prawns. In contrast, the metal concentrations were similar in raw and cooked Greenlandic halibut and Arctic salmon [134].

Conclusion

Eleven metals were measured in a Greenlandic adult population. The metal concentrations differed generally by sex, residential town, marine intake (*n*-3/*n*-6 FA ratio), and socio-economic factors. Furthermore, As, Hg, and Se were associated positively with intake of traditional marine food. Few other associations were seen between metal concentrations and food intake. A high percentage of the study population (25–45%) exceeded the international guidance values for Hg indicating a potential risk of health effects related to Hg exposure and the need to follow-up on the sources and exposure. To our knowledge, in Greenlandic Inuit, the changes in intra-individual metal concentrations have not been reported before. Interestingly, all metals changed significantly in mothers from inclusion at pregnancy of the ACCEPT mothers (2013–15) to this follow-up study 3–5 years after giving birth. Some metals/elements increased (Fe, Mg, Se, Zn, As, Hg, and Pb) while others decreased (Ca, Cu, Mn, and Cd). We cannot fully explain the changes observed in present study, and for elucidation, further investigations are needed.

Abbreviations

As	arsenic
BMI	body mass index
Ca	calcium
Cd	cadmium
CI	Confidence interval

Cu	copper
Dancea	Danish Cooperation for Environment in the Arctic
FA	Fatty acid
Fe	iron
FFQ	food frequency questionnaire
Hg	mercury
KMO	Kaiser-Meyer-Olkin
LOD	limit of detection
Mg	magnesium
Mn	manganese
P	Plasma
Pb	lead
PC	principal component
PCA	principal components analysis
Se	selenium
WB	Whole blood
Zn	zinc

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Ethics approval

The Commission for Scientific Investigations in Greenland (KVUG 2019–04) approved the study.

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