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Concentrations of cadmium, cobalt, chromium, manganese, nickel, and iodine in urine from first-time mothers in Uppsala, Sweden: temporal trends 2009-2020

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Sammanfattning

Sedan 1996 samlas blod- och modersmjölksprover regelbundet in från förstföderskor i Uppsala i den så kallade POPUP-studien. Sedan 2009 tas också ett urinprov. I denna rapport har tidstrender för kadmium, kobolt, krom, mangan, nickel och jod studerats i urinprov (n=371) insamlade mellan 2009 och 2020. Resultaten visade inte någon trend för kadmium vilket stämmer överens med andra studier. För nickel och krom sågs en nedåtgående trend med i medeltal 8,8 respektive 3,5 % per år. Kadmiumhalterna i denna studie var på samma nivå som hos medelålders svenska kvinnor (50-59 år) och något högre än i andra studier från Sverige på gravida kvinnor och kvinnor i åldern 19-39 år. Totalt 25 av de 371 mammorna (7%) hade halter över 0.5 µg/g kreatinin, vilket är den nivå som anses kunna öka risken för påverkan på skelettet. Alla deltagare i studien hade precis genomgått en graviditet vilket kan påverka resultaten, t ex är det vanligt med låga järnnivåer under graviditet som i sin tur kan öka upptaget av kadmium.

Kadmium-halter i urin från rökare och före-detta rökare var högre jämfört med kvinnor som uppgett att de inte var rökare. Detta resultat stämmer väl med andra studier. Halter av kadmium, kobolt och jod var högre bland vegetarianer, alltså kvinnor som uppgett att de inte äter animaliskt kött, jämfört med kvinnor som äter kött. Högre halter av kadmium och kobolt kan bero på låg järnstatus och som är vanligare hos vegetarianer.

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INTRODUCTION

The Swedish Food Agency has conducted recurrent sampling of breastmilk and blood from primiparous women in Uppsala since 1996, in the so-called POPUP study (Persistent Organic Pollutants in Uppsala Primiparas). The Swedish Environmental Protection Agency has funded the study since the year 2000. The main aim of the study is to investigate temporal trends of exposure to persistent organic pollutants (POP) among pregnant and nursing women. Since 2009, urine samples are collected from the women in POPUP three weeks after delivery. In the present study, cadmium, cobalt, chromium, nickel and iodine were analysed in urine samples collected 2009-2020. This is the first time that temporal trends of elements have been investigated within the POPUP study. Of main concern among the analysed elements is cadmium. Cadmium is a metal that is toxic to the kidneys, bone, testicles and recent studies also found associations between cadmium exposure and cardiovascular diseases (Barregård et la. 2021).

Cadmium is a metal naturally occurring in the soil at low levels. It is also continually added to the soil through sewage sludge, air pollution and cadmium contaminated fertilizer (Järup and Åkesson, 2009). Food is the main source of cadmium exposure in the general population, but smoking can be a major contributing factor. Smokers have, on average, 4-5 times higher cadmium levels compared to non-smokers due to high concentrations of cadmium in tobacco leaves and a higher absorption of cadmium through the lungs compared to the gastrointestinal tract (Satarug and Moore, 2004). Cadmium accumulates slowly in the body and the highest levels are found in the kidneys,and is reflected in the urinary cadmium concentration. The European Food Safety Authority (EFSA) has established a tolerable weekly intake (TWI) for cadmium from food of 2.5 µg/kg body weight (bw)/week which is related to a critical urinary concentration of 1 µg/g creatinine after around 50 years of exposure (EFSA, 2009). However, recent studies have observed negative effects on the skeleton at urine concentrations of 0.5 µg/g creatinine (Järup and Åkesson, 2009, Åkesson et al. 2014).

Ingested cadmium is absorbed in the gastrointestinal tract through the same mechanism as iron. This makes cadmium absorption higher when iron status is low. Several studies have shown that cadmium concentrations in blood and urine are increased at lower iron levels (Åkesson et al. 2002, Julin et al. 2011, Bjermo et al. 2013a). Cereal products are the largest source of cadmium in food, but potatoes and other root-vegetables also contribute significantly to the exposure. There are also certain foods that may contribute disproportionally but are seldom consumed, such as the prince/horse mushroom and brown crab meat (Livsmedelsverket, 2017). According to the Swedish market basket survey the estimated weekly mean intake per capita in Sweden is 1.3 µg cadmium/kg bw (Livsmedelsverket, 2017).

Cobalt is included in the essential vitamin B12 complex and is therefore considered as an essential trace element (Gad, 2014). Higher cobalt levels in blood have been found in women with low iron stores, which is related to the common absorption and transport mechanisms of iron and cobalt (Meltzer et al., 2010). The main exposure sources of cobalt are through inhalation and ingestions of food and drinking water (ATSDR, 2004). The estimated mean per capita intake of cobalt in Sweden is around 11 µg/day (Livsmedelsverket, 2017). The toxicity of cobalt includes its ability to inhibit different enzymes for example those involved in the cellular respiration. Also, cobalt inhibits the iodine metabolism resulting in reduced thyroid activity (Gad, 2014).

Chromium is naturally occurring in air, water and soil and is ubiquitous in food. The role of chromium as an essential nutrient for humans is still unclear. EFSA has set a TDI of 300 µg/kg bw/day for chromium in trivalent form (Cr(III)) based on the lowest NOAEL identified in a chronic oral toxicity study in rats (EFSA, 2014). EFSA has not set any average requirement due to lack of evidence. The estimated mean per capita intake of chromium in Sweden is around 41 µg/day (Livsmedelsverket, 2017).

Manganese is an essential element and is needed for many biological functions such as protein synthesis. The main source is food, such as rice, oatmeal and leafy vegetables, and drinking water. Manganese and iron share absorption pathway (Nielsen, 2012), hence, blood manganese concentrations have been found elevated at iron deficiency (Kim et al. 2005). High exposure to manganese can cause toxic neurological effects (ATSDR, 2012). Adequate intake is estimated to 3 mg/day for adults (EFSA, 2013) and normal manganese levels in urine are 1–8 µg/L (ATSDR, 2012). The estimated mean per capita intake of manganese in Sweden is around 4.2 mg/day (Livsmedelsverket, 2017).

Nickel is a trace element found in small amounts in food. The function of nickel in the body is not fully understood. Nickel has a tolerable daily intake of 13 µg/kg bw based on developmental effects in rats. However, for nickel-sensitised individuals it can cause eczematous flare-ups acutely, and the lowest observed adverse effect level (LOAEL) for this effect is 4.3 µg/kg bw (EFSA 2020). The estimated mean per capita intake of nickel exposure in Sweden is around 133 µg/day, which equates to 1.7 µg/kg bw/day (Livsmedelsverket, 2017).

Iodine is required for the synthesis of thyroid hormones and foods like lean fish, shellfish, eggs and dairy products contain a lot of iodine. Iodized table salt is also an important source of iodine. The recommended daily intake is 150 µg/dag for adults, 175 µg/day for pregnant women and 200 µg/day for breastfeeding women (NNR, 2014). Based on data from the Swedish market basket survey, the estimated mean per capita intake of iodine in Sweden is around 92 µg/day (Livsmedelsverket, 2017). This intake is however an underestimate since the market basket survey does not include iodized salt. An upper limit of 600 µg is set by The Scientific Committee on Food (SCF, 2006). EFSA considers that a urinary concentration of less than 100 µg/L indicates an inadequate iodine intake (Efsa, 2014).

MATERIALS AND METHODS

Recruitment and sampling

Participants were randomly recruited among first-time mothers who were Swedish by birth and delivered at Uppsala University Hospital. Thirty women participated every year between 2009 and 2020, except for 2019 when 50 mothers were recruited. The participation rate was 47%. Spot urine samples were collected three weeks after delivery. Demographic data on age, weight, height, and lifestyle and food habits etc. of the mothers were obtained from questionnaires. The present study includes urine samples from 371 women.

Analytical procedure

Prior to analysis, the urine samples were diluted 20-fold with an alkaline solution according to Barany et al. (1997) and all samples were prepared in duplicate. The concentrations of metals were determined by inductively coupled plasma mass spectrometry (ICP-MS; iCAP Q, Thermo Fisher Scientific, Bremen, GmbH, Germany) equipped with collision cell with kinetic energy discrimination and helium as the collision gas in peak-jumping mode. The limit of detection (LOD) was calculated as three times the standard deviation for the blank. The method imprecision was calculated as the coefficients of variation in measurements of duplicate preparations. Certified reference materials were routinely analysed among the samples to ensure the analytical quality. The reference materials were obtained from The German External Quality Assessment Scheme, Erlangen Germany (G-EQUAS R66), material 7A/B and 1A. There was good agreement between known and measured concentrations in the reference materials (Table 1). The analyses were performed at the Division of Occupational and Environmental Medicine, Lund University, Sweden.

Table 1. *Limit of detection (LOD) and Quality control data for the measurements.*

Element	**LOD**	**Imprecision**	**Reference samples**[a]	
			Measured Mean ±SD	**Target Value (Accepted range)**
	(µg/L)	**(%)**	**(µg/L)**	**(µg/L)**
Cadmium (Cd)	0.01	5.3	0.21 ±0.01 1.11 ±0.21 2.35 ±0.07	0.20 (0.08-0.32)[b] 1.06 (0.85-1.27)[c] 2.33 (1.97-2.69)[d]
Cobalt (Co)	0.02	5.1	4.4 ±0.20	4.3 (3.4-5.2)[d]
Chromium (Cr)	0.08	17	0.32 ±0.05 0.98 ±0.22 9.8 ±0.41	0.36 (0.21-0.51)[b] 0.99 (0.81-1.17)[c] 9.7 (8.2-11.2)[d]
Manganese (Mn)	0.06	14	4.9 ±0.14	5.2 (4.3-6.1)[d]
Nickel (Ni)	0.25	5.4	0.94 ±0,10 3.1 ±0,67 11.5 ±0.71	0.98 (0.65-1.31)[b] 3.0 (2.4-3.5)[c] 11.3 (9.2-13.4)[d]
Iodine (I)	0.60	3.5	86 ±5.8	86 (76-96)[d]

[a]n = 66
[b]G-EQUAS R66 7A
[c]G-EQUAS R66 7B
[d]G-EQUAS R66 1A

Calculations and statistics

Statistical analyses were performed using the software package STATA version 15.1. When urine concentrations were below LOD, the reported urine concentrations were used (i.e. the blank concentration was subtracted from the measured concentration of the sample). Correlations between density adjusted urine concentrations of the different elements were tested with Spearman's rank correlation test. Temporal trends were investigated for the study period 2009-2020. Linear regressions were used to analyse associations between ln-transformed density-adjusted urine concentrations and sampling year. Multiple linear regression analyses including the covariates age, pre-pregnancy body mass index (BMI), weight gain during pregnancy (%), weight loss from delivery to time of sampling (%), education, smoking, vegetarian diet, and season of sampling were also conducted. Observations with standardized residuals ≥3 were regarded as outlier and omitted in these tests. As a consequence of the logarithmic transformation, the associations between sampling year and urine concentrations are presented as percent change of concentrations per year, and not as change in absolute levels. For different smoking and vegetarian categories, adjusted means, of density adjusted urine concentrations, were calculated and compared using ANCOVA and a linear model. The means and 95% confidence interval were adjusted for age, pre-pregnancy BMI, weight gain during pregnancy, weight loss after delivery, education, sampling year and season.

RESULTS AND DISCUSSION

Characteristics of the first-time mothers with urine samples 2009-2020 are shown in Table 2.

Table 2. *Population characteristics (N=371).*

Variable		**Mean ± SD**	**(Min-Max)**
Age (year)		30 ± 4	(20-45)
Pre-pregnancy body mass index (BMI, kg/m^2)		23 ± 4	(17-44)
Weight gain during pregnancy (%)		24 ± 9	(-6-57)
Weight reduction from delivery to sampling (%)		9 ± 3	(-1-18)
Urine creatinine (mmol/L)		7.7 ± 4.1	(0.60-25.8)
Urine density (g/L)		1.015 ± 0.006	(1.003-1.039)
Variable		**N**	**(%)**
Education	Max 3-4 years of high school	57	(15%)
	1-3 years of higher education	78	(21%)
	>3 years of higher education	236	(64%)
Smoking[a]	Non-smoker	290	(78%)
	Former smoker	67	(18%)
	Smoker	14	(4%)
Vegetarian diet[b]	No	322	(90%)
	Yes	35	(10%)
Season for sampling	Spring	106	(29%)
	Summer	47	(13%)
	Autumn	140	(38%)
	Winter	78	(21%)

[a]Women who stopped before pregnancy are considered to be former smoker. Women who smoked during pregnancy are defined as smoker even if they stopped during the first or second month of pregnancy.
[b]Women that have answered that they are not eating animal meat were considered as vegetarians.

Urine concentrations of the analysed compounds are presented in Table 3. Both reported concentrations and concentrations adjusted for urine density and creatinine are included. Cadmium, cobalt, nickel and iodine had detectable concentrations in all samples or only a few samples with concentrations below LOD whereas chromium and manganese had undetected levels in 13% and 39% of the samples, respectively (Table 3).

The cadmium concentrations in these first-time mothers (median 0.16 µg/L and 0.20 µg/g creatinine) were in the same range as in Swedish women at 50-59 years of age (median 0.18 µg/L) (Kippler et al. 2020), but somewhat higher compared to pregnant women from northern Sweden (median 0.10 µg/L) (Gustin et al, 2021) and also higher compared to 19-29 and 30-39 year old women in the Riksmaten biomonitoring study (median 0.09 and 0.10 µg/g creatinine, respectively) (Bjermo et al. 2013b) and women aged 20-29 from Stockholm (median 0.17 µg/g creatinine (Berglund et al. 2010). The risk assessment of cadmium conducted by EFSA established a TWI based on a urinary concentration of 1 µg/g creatinine after around 50 years of exposure to protect from negative effects on the kidneys (EFSA, 2009). However, negative effects on the skeleton have been observed at urine concentrations of 0.5 µg/g creatinine (Järup and Åkesson, 2009, Åkesson et al. 2014). Furthermore, newly developed human biomonitoring guidance values for cadmium has set the threshold in urine to 0.3 and 0.5 µg/g creatinine for the age groups of 21-30 and 31-40, respectively (Lamkarkach et al. 2021). In the present study, one woman had urine concentrations above 1 µg/g creatinine and 25 women (7%) had concentrations above 0.5 µg/g creatinine. The relatively high levels of cadmium in this study could be due to that all women were sampled 3 weeks after delivery. High levels could be expected because cadmium and iron share absorption pathway and iron depletion is common during pregnancy. It has been shown that women who had their iron stores depleted during pregnancy had increased urinary cadmium after the pregnancy (Åkesson et al. 2002).

The levels of cobalt were lower and for nickel higher in the present study, compared to a study of women in third trimester from Spain, sampled 2003-2008 (geometric mean 1.1 and 1.7 µg/g creatinine, respectively) (Lozano et al. 2022). Median levels of cobalt and manganese were also lower in the present study compared to women from the U. S, sampled in 2011-2012, from the National Health and Nutrition Examination Survey (NHANES) (median 0.43 and 0,16 µg/g creatinine, respectively) (CDC, 2017). Median urine levels of chromium were below LOD (0.19 µg/L) in women sampled 2017-2018 from NHANES and could not be compared to the levels in the present study with a lower LOD (0.08 µg/L) (CDC, 2022).

The median urinary iodine concentration in the present study (56 µg/L) was about half of the median concentrations in women sampled during pregnancy in northern Sweden, 2015-2018 (113 µg/L) (Stråvik et al, 2021) and in Finland in 2013-2017 (120 µg/L) (Miles et al. 2022). In the Finnish study, the median urine iodine concentration was lower 3 months postpartum than during pregnancy (89 vs 120 µg/L), but still higher than in the present study. We speculate that the low measured levels of iodine in the POPUP participants may be due to the recent delivery. EFSA considered that a urine concentration less than 100 µg/L indicates insufficient iodine intake (EFSA, 2014) and in the present study, 321 women (87%) had levels below that. Sufficient iodine levels are particularly important during pregnancy. Severe iodine deficiency in pregnant women may cause mental retardation in the child, but mild deficiency has also been suggested to be associated with developmental impairment (NNR 2014).

The correlation analysis showed low but significant correlations between cadmium and cobalt and also between cadmium and manganese (Table 4). It is known that low iron storage trigger the uptake of cadmium (Åkesson et al. 2002), cobalt (Meltzer et al. 2010) and manganese (Nielsen, 2012) due to shared absorption and transport mechanisms. Low iron storage might therefore contribute to the observed correlations as all women in the present study were sampled 3 weeks after delivery of their first child. Significant correlations were also observed for chromium and manganese, chromium and nickel, and cobalt and nickel, although the correlations were rather weak, Spearman´s correlation coefficients 0.27-0.42 (Table 4).

Table 3. *Urine concentrations (ng/mL) of elements in first-time mothers between 2009 and 2020. Both reported, density-adjusted (ng/mL), mol creatinine-adjusted (µmol/mol creatinine), and g creatine-adjusted (µg/g creatinine) concentrations are presented (N=371).*

Elements		**Mean (SD)**	**Median**	**95% percentile**	**Min-Max**	**N(%) <LOD**	**LOD (ng/mL)**
Cadmium	raw	0.21 (0.20)	0.16	0.53	0.02-1.87	0 (0)	0.01
	dens. adj	0.21 (0.16)	0.16	0.51	0.04-1.31		
	crea mol adj	0.24 (0.15)	0.21	0.56	0.05-1.01		
	crea g adj	0.24 (0.15)	0.20	0.55	0.05-1.01		
Cobalt	raw	0.42 (0.55)	0.24	1.25	0.03-4.95	0 (0)	0.02
	dens. adj	0.39 (0.37)	0.27	1.03	0.05-3.47		
	crea mol adj	0.89 (0.81)	0.63	2.31	0.18-7.21		
	crea g adj	0.46 (0.42)	0.33	1.20	0.10-3.75		
Chromium	raw	0.23 (0.19)	0.19	0.56	0.003[a]-1.47	47 (13)	0.08
	dens. adj	0.26 (0.27)	0.18	0.67	0.004[a]-2.93		
	crea mol adj	0.70 (0.85)	0.48	1.88	0.01[a]-8.13		
	crea g adj	0.32 (0.39)	0.22	0.86	0.005[a]-3.74		
Manganese	raw	0.17 (0.47)	0.07	0.49	0.005[a]-7.44	144 (39)	0.06
	dens. adj	0.20 (0.50)	0.08	0.76	0.005[a]-5.31		
	crea mol adj	0.52 (1.53)	0.20	1.58	0.01[a]-15.8		
	crea g adj	0.25 (0.74)	0.09	0.77	0.005[a]-7.69		
Nickel	raw	3.55 (5.73)	1.62	15.5	0.22[a]-45.7	3 (1)	0.25
	dens. adj	4.15 (9.18)	1.65	18.3	0.47[a]-124		
	crea mol adj	10.5 (26.3)	3.83	52.0	0.80[a]-371		
	crea g adj	5.46 (13.7)	1.99	27.0	0.42[a]-192		
Iodine	raw	67.4 (50.2)	55.5	157	5.70- 558	0 (0)	0.60
	dens. adj	68.9 (46.6)	57.7	141	17.8-578		
	crea mol adj	76.6 (66.2)	62.2	163	16.7-1023		
	crea g adj	86.0 (74.2)	69.7	182	18.7-1148		

SD = standard deviation, LOD = limit of detection.
[a]Reported concentration below LOD.

Table 4. *Spearman's correlation between density adjusted urine concentrations (N=371).*

	Cadmium	Cobalt	Chromium	Manganese	Nickel	Iodine
Cadmium	1					
Cobalt	**0.21 p< 0.001**	1				
Chromium	0.12 p=0.36	0.02 p=1.0	1			
Manganese	**0.28 p< 0.001**	0.003 p=1.0	**0.30 p< 0.001**	1		
Nickel	0.04 p=1.0	**0.27 p< 0.001**	**0.42 p< 0.001**	0.13 p=0.18	1	
Iodine	0.04 p=1.0	0.11 p=0.53	0.06 p=1.0	0.08 p=1.0	0.11 p=0.45	1

Temporal trends

Temporal trends for the analysed elements are presented in Table 5, both from univariate analyses and multivariate analyses adjusted for possible temporal changes in personal characteristics. Urine levels (medians and 95% CI) for each sampling year are shown in Figure 1. No temporal trend was observed for cadmium which are in agreement with other studies within the Health-related environmental monitoring program (HÄMI) reporting no trends for cadmium in urine from women at age 20–29 and 50–59, in Skåne, Västra Götaland, Stockholm and Norr- and Västerbotten (2002-2018) and for cadmium serum levels in children (1990-2014) (NV/IMM, 2022).

The results for chromium and nickel show that urine levels have decreased during the study period 2009-2020 with a mean decrease of 8.8% and 3.5% per year, respectively. No temporal trend was observed for cobalt, manganese and iodine. No temporal trend in urine concentrations of nickel was observed in Germans students (age 20-29) sampled 2002-2009 (Becker et al. 2013). To our knowledge no other temporal trends in urine concentrations of chromium and nickel have been published and the reasons for the decreasing trends in the present study are unknown. Per capita intakes estimated from the Swedish market basket survey showed similar intakes of chromium and nickel in 2010 and 2015 (Livsmedelsverket, 2017).

Table 5. *Annual change in urine levels of elements (density-adjusted) in first-time mothers between 2009 and 2020 (N=371).*

	Univariate analysis			**Multivariate analysis[a]**				
	Change per year				**Change per year**			
Elements	**Mean (%)**	**95% CI**	**p**	**n**	**Mean (%)**	**95% CI**	**p**	**R^2 (%)**
Cadmium	0.9	-0.9/2.7	0.34	366	0.6	-1.1/2.5	0.49	8.7
Cobalt	-0.6	-2.6/1.4	0.54	366	-0.3	-2.3/1.8	0.80	8.5
Chromium	**-3.0**	**-0.9/-5.1**	**0.006**	363	**-3.5**	**-1.5/-5.5**	**0.001**	**4.7**
Manganese	-2.7	-5.3/0.03	0.052	359	-2.0	-4.5/0.5	0.12	3.3
Nickel	**-8.1**	**-5.7/-10.5**	**<0.001**	364	**-8.8**	**-6.4/-11.1**	**<0.001**	**15.5**
Iodine	0.4	-1.8/1.0	0.56	366	-0.9	-2.3/0.5	0.21	10.7

[a]Adjusted for maternal age, pre-pregnancy body mass index (BMI), weight gain during pregnancy, weight loss from delivery to time of sampling, education, smoking, vegetarian diet, and season of sampling.

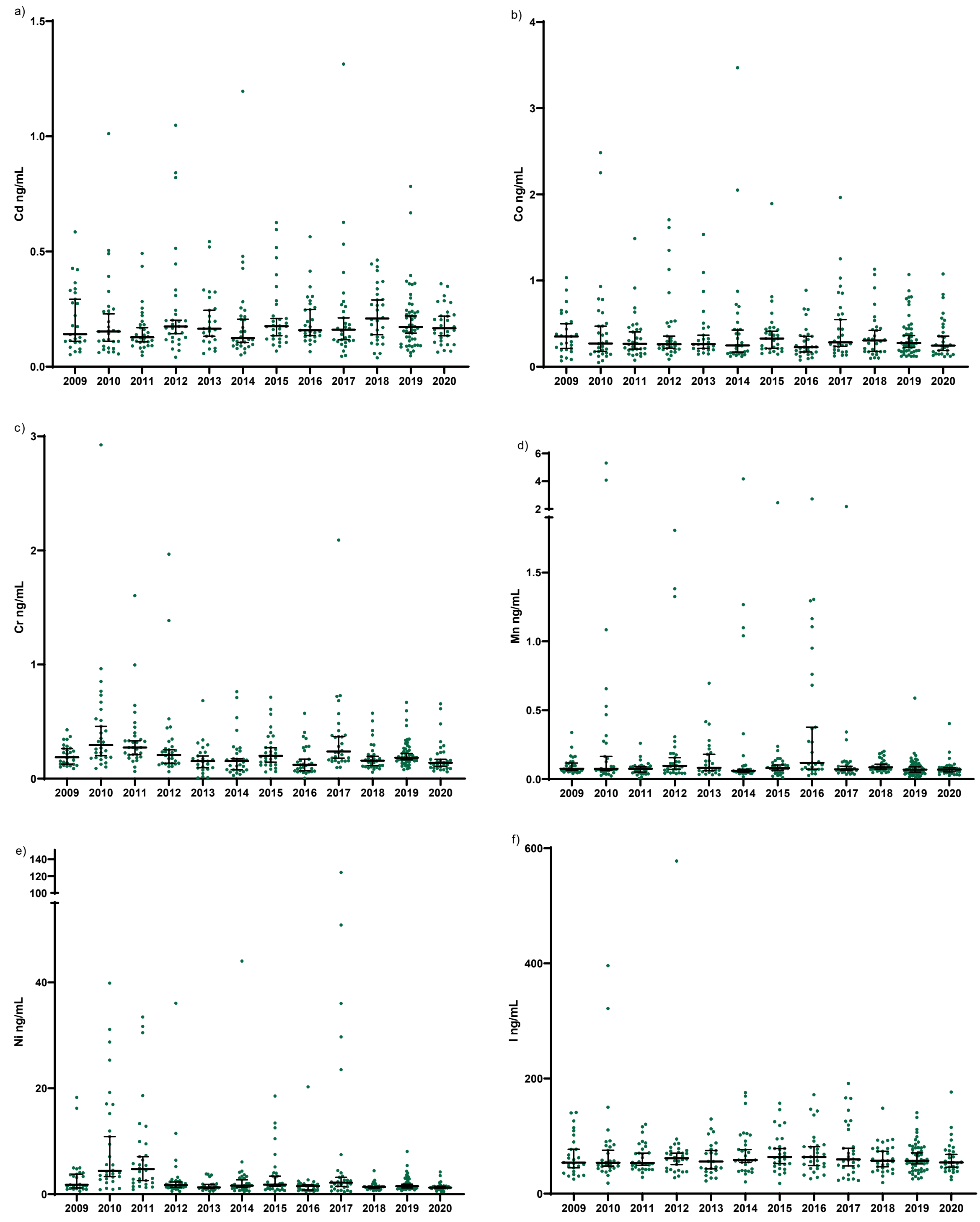

Figure 1. *Density adjusted levels (median and 95% CI) of Cadmium (a), Cobalt (b), Chromium (c), Manganese (d), Nickel (e), and Iodine (f) in urine samples from first-time mothers, sampled three weeks after delivery during 2009-2020, N=371.*

Associations with smoking and vegetarian diet

Adjusted mean urine concentrations of cadmium were significantly higher among smokers and former smokers compared with non-smokers (Figure 2). Among mothers with cadmium levels above 0.5 µg/g creatinine, 58% were non-smokers and among mothers with lower levels 80% were non-smokers. Since tobacco smoking is known to contribute to cadmium exposure (EFSA, 2009) the observed difference was expected.

Adjusted mean urine concentrations of cadmium, cobalt and iodine were significantly higher among vegetarians compared with non-vegetarians (Figure 2). Among the mothers with cadmium levels above 0.5 µg/g creatinine, 18% were vegetarians and among mothers with lower levels 9% were vegetarians. Higher cadmium levels in vegetarians could be due to lower iron status (Haider et al. 2018) and a subsequent increased cadmium uptake (EFSA, 2009). In addition, vegetarian food such as grains, potatoes and vegetables contain much higher levels of cadmium than animal products. According to the Swedish market basket survey, cereal products and potatoes both contain around 25µg cadmium/kg in median, whereas meat and fish had median levels around 2-5 µg/kg (Livsmedelsverket, 2017).

The higher levels of cobalt seen among vegetarians might be explained by low iron status among vegetarians or higher levels of cobalt in vegetarian food than in animal based food (Livsmedelsverket, 2017). Iron deficiency or depleted iron stores are common among vegetarians (Haider et al. 2018, Sebastiani et al. 2019) but also among pregnant women (Åkesson et al. 2002) and in an iron deficient state cobalt absorption is enhanced (Meltzer et al. 2010).

Higher iodine levels in vegetarians was however not expected since previous studies have indicated that vegetarians have low levels of iodine and are recommended iodine supplementation (Weikert et al. 2020, Schuepbach et al. 2017, Groufh-Jacobsen etal. 2020). In a study of pregnant women from northern Sweden the number of participants using supplements was significantly higher in the group with high levels of urinary iodine compared with those with low levels of iodine (Stråvik et al. 2021). In the same study it was also observed that women who used iodized table salt during pregnancy had higher levels of urinary iodine compared with those who used non-iodised table salt (Stråvik et al. 2021). The number of vegetarians did not differ between the high and low iodine group, however the study of pregnant women from northern Sweden had only 2% vegetarians, compared to 10% in the present study (Stråvik et al. 2021). It is difficult to explain higher iodine concentrations in vegetarians in the present study. However, it may be due to chance or possibly due to a higher use of iodine supplements in vegetarians.

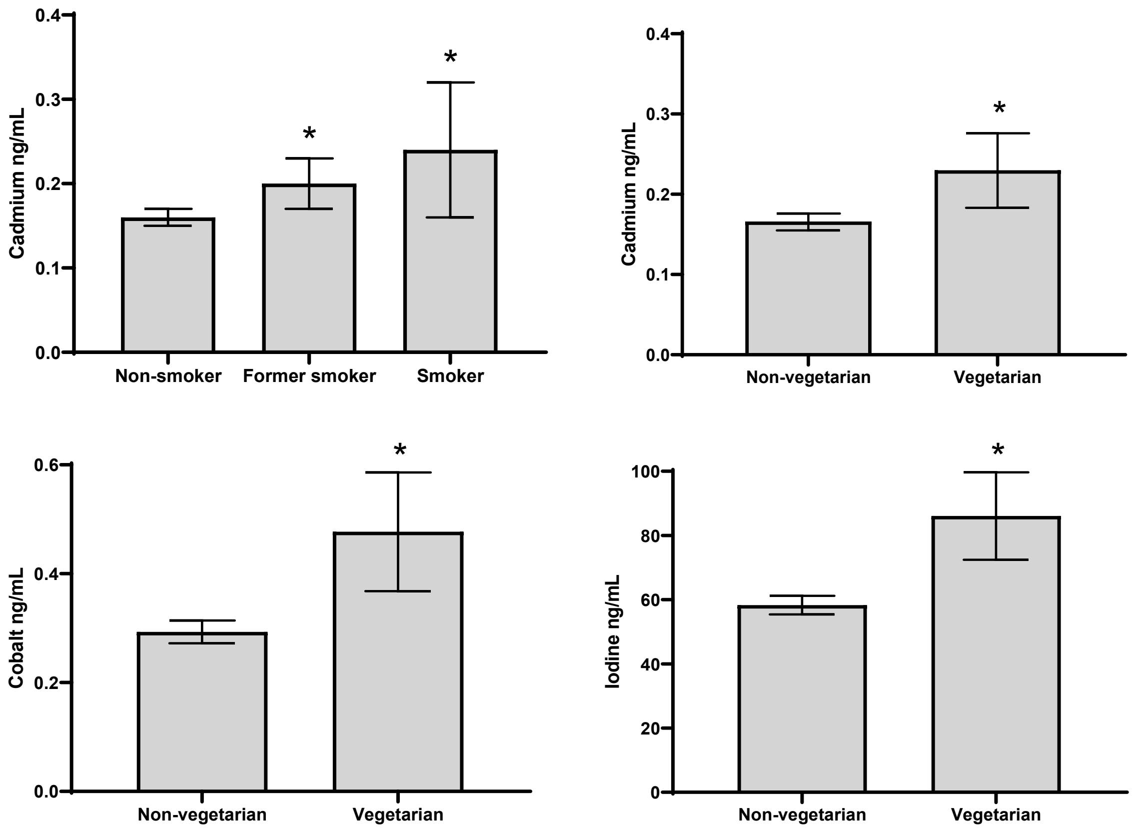

Figure 2. *Adjusted means (95% confidence interval) of urine concentrations in mothers samples 2009-2020 according to smoking and vegetarian diet. The means were calculated and compared using ANCOVA and a linear model, and were adjusted for age, pre-pregnancy BMI, weight gain during pregnancy, weight loss after delivery, education, sampling year and season. Non-smoker N=290, former smoker N=67, smoker N=14, non-vegetarian N=322, vegetarian N=35. *=significantly different (p<0.05) from non-smoker or non-vegetarian.*

CONCLUSION

In agreement with other biomonitoring studies in Sweden, no trend was observed for cadmium urine levels in first-time mothers sampled 2009-2020. The concentrations of cadmium were however relatively high and in the same range as in older Swedish women (50-59 years), possibly due to that all women were sampled 3 weeks after their first pregnancy. About 7% of the mothers had levels above 0.5 µg/g creatinine where negative effects on the skeleton have been observed.

The only temporal trends observed were decreasing levels of chromium and nickel. The reason for this is unclear. Notable was the low urinary iodine levels. This is not uncommon but highlights the importance of maintaining appropriate iodine levels during pregnancy.

Cadmium levels in urine from smokers and former smokers showed, as expected, higher levels compared to women who stated that they were non-smokers. Levels of cadmium, cobalt and iodine were higher in vegetarians. Higher levels of cadmium and cobalt may be due to low iron status, which is more common in vegetarians.

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REFERENCES

ATSDR 2004. Agency for Toxic Substances and Disease Registry, Toxicological profile for cobalt. Atlanta, U.S.: U.S. Department of Health and Human Services, Public Health Service; 2004

ATSDR 2012. Agency for Toxic Substances and Disease Registry, Toxicological profiles Manganese. https://www.atsdr.cdc.gov/toxprofiles/tp151-c2.pdf

Barany E, Bergdahl I, Schütz A, Skerfving S, Oskarsson A. 1997. Inductively coupled plasma mass spectrometry for direct multi-element analysis of diluted human blood and serum. J. Anal. At. Spectrom. 12, 1005.

Barregård L, Sallsten G, Harari F, Andersson EM, Forsgard N, Hjelmgren O, Angerås O, Fagman E, Persson M, Lundh T, Borné Y, Fagerberg B, Engström G, Bergström G. 2021. Cadmium Exposure and Coronary Artery Atherosclerosis: A Cross-Sectional Population-Based Study of Swedish Middle-Aged Adults. Environ Health Perspect 129(6):67007.

Becker K, Schroeter-Kermani C, Seiwert M, Rüther M, Conrad A, Schulz C, Wilhelm M, Wittsiepe J, Günsel A, Dobler L, Kolossa-Gehring M. 2013. German health-related environmental monitoring: assessing time trends of the general population's exposure to heavy metals. Int J Hyg Environ Health 216(3):250-254.

Berglund M, Palm B, Åkesson A. 2010. Cadmium exposure in a risk group. Rapport Naturvårdsverket

Bjermo H, Sand S, Nalsen C, Lundh T, Enghardt Barbieri H, Pearson M, Lindroos AK, Jonsson BA, Barregard L, Darnerud PO. 2013a. Lead, mercury, and cadmium in blood and their relation to diet among Swedish adults. Food Chem Toxicol, 57, 161-169.

Bjermo H, Ax E, Cantillana T, Glynn A, Darnerud PO, Lindroos AK. 2013b. Miljöföroreningar i blod och urin och kopplingar till rapporterat matintag i Riksmaten 2010-11 – resultatsammanställning. Rapport Naturvårdsverket

CDC 2017. Centers for Disease Control and Prevention. Fourth National Report on Human Exposure to Environmental Chemicals. Updated Tables, January 2017, Volume One.

CDC 2022. Centers for Disease Control and Prevention. Urinary Chromium (2017 - 2018). https://www.cdc.gov/exposurereport/report/pdf/cgroup7_URXUCM_2011-p.pdf

EFSA 2009. Scientific Opinion, Cadmium in food. The EFSA Journal.

EFSA 2013. Scientific Opinion on Dietary Reference Values for manganese. The EFSA Journal.

EFSA 2014. Scientific Opinion on Dietary Reference Values for iodine. The EFSA Journal.

EFSA 2020. Scientific Opinion, Update of the risk assessment of nickel in food and drinking water. The EFSA Journal.

Gad S.C. 2014. Encyclopedia of Toxicology (Third Edition), Pages 996-998.

Gustin K, Barman M, Skröder H, Jacobsson B, Sandin A, Sandberg AS, Wold AE, Vahter M, Kippler M. 2021. Thyroid hormones in relation to toxic metal exposure in pregnancy, and potential interactions with iodine and selenium. Environ International 157: 106869

NV/IMM 2022. IMM, Hälsorelaterad miljöövervakning, Tidsserier och data https://ki.se/imm/tidsserier-och-data

Haider LM, Schwingshackl L, Hoffmann G, Ekmekcioglu C. 2018. The effect of vegetarian diets on iron status in adults: A systematic review and meta-analysis. Crit Rev Food Sci Nutr 58(8):1359-1374.

Julin B, Vahter M, Amzal B, Wolk A, Berglund M, Akesson A. 2011. Relation between dietary cadmium intake and biomarkers of cadmium exposure in premenopausal women accounting for body iron stores. Environ Health, 10, 105.

Järup L, Åkesson A. 2009. Current status of cadmium as an environmental health problem. Toxicol Appl Pharmacol 238:201-208.

Kim Y, Park JK, Choi Y, Yoo CI, Lee CR, Lee H, Lee JH, Kim SR, Jeong TH, Yoon CS, Park JH. 2005. Blood manganese concentration is elevated in iron deficiency anemia patients, whereas globus pallidus signal intensity is minimally affected. Neurotoxicology 26(1):107–111.

Kippler M, Broberg K, Wennberg M, Hovgard A, Sällsten G, Assarsson E, Lundh T. 2020. Biomonitorering av kadmium i urin hos svenska och utländska kvinnor. Rapport Naturvårdsverket

Lamkarkach F, Ougier E, Garnier R, Viau C, Kolossa-Gehring M, Lange R, Apel P. 2021. Human biomonitoring initiative (HBM4EU): Human biomonitoring guidance values (HBM-GVs) derived for cadmium and its compounds. Environ Int 147:106337.

Livsmedelsverket 2017. Swedish Market Basket Survey 2015. Livsmedelsverkets rapportserie nr 26/2017. Uppsala, Sweden: Livsmedelsverket.

Lozano M, Murcia M, Soler-Blasco R, Casas M, Zubero B, Riutort-Mayol G, Gil F, Olmedo P, Grimalt JO, Amorós R, Lertxundi A, Vrijheid M, Ballester F, Llop S. 2022. Exposure to metals and metalloids among pregnant women from Spain: Levels and associated factors. Chemosphere 286(Pt 2):131809

Meltzer HM, Branstæter AL, Borch-Iohnsen B, Ellingsen DG, Alexander J, Thomassen Y, Stigum H, Ydersbond TA. 2010. Low iron stores are related to higher blood lead concentrations of manganese, cobalt and cadmium in non-smoking, Norwegian women in the HUNT2 study. Environ Res 110:497–504.

Miles EA, Vahlberg T, Calder PC, Houttu N, Pajunen L, Koivuniemi E, Mokkala K, Laitinen K. 2022. Iodine status in pregnant women and infants in Finland. Eur J Nutr. In print.

Nielsen FH. 2012. Manganese, Molybdenum, Boron, Chromium, and Other Trace Elements. In: John W. Erdman Jr. IAM, Steven H. Zeisel, ed. Present Knowledge in Nutrition. 10th ed: Wiley-Blackwell, 586-607.

NNR 2014. Nordic Nutrition Recommendations 2012, Integrating nutrition and physical activity, Copenhagen, Nordic Council of Ministers.

Satarug S, Moore MR. 2004. Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke. Environ Health Perspect, 112, 1099-1103.

SCF 2006. The Scientific Committee on Food, Tolerable Upper intake Levels for Vitamins and Minerals.

Sebastiani G, Herranz Barbero A, Borrás-Novell C, Alsina Casanova M, Aldecoa-Bilbao V, Andreu-Fernández V, Pascual Tutusaus M, Ferrero Martínez S, Gómez Roig MD, García-Algar O. 2019. The Effects of Vegetarian and Vegan Diet during Pregnancy on the Health of Mothers and Offspring. Nutrients 11(3):557.

Stråvik M, Gustin K, Barman M, Skröder H, Sandin S, Wold AE, Sandberg AS, Kippler M, Vahter M. 2021. Infant Iodine and Selenium Status in Relation to Maternal Status and Diet During Pregnancy and Lactation. Front Nutr. 8:733602.

Åkesson A, Berglund M, Schütz A, Bjellerup P, Bremme K, Vahter M. 2002. Cadmium exposure in pregnancy and lactation in relation to iron status. American Journal of Public Health 92(2):284-287.

Åkesson A, Barregard L, Bergdahl IA, Nordberg GF, Nordberg M, Skerfving S. 2014. Non-renal effects and the risk assessment of environmental cadmium exposure. Environ Health Perspect 122(5):431-438.