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Descriptive analysis of whole blood concentrations of toxic, essential, and trace elements in adult females from the MIREC-ENDO study

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ABSTRACT

Background: Exposure to toxic elements and deficiencies/excessive exposure to essential elements is associated with adverse health effects. Robust biomonitoring data exist for select elements in the general population of Canada, but data are limited for several essential/trace elements, especially among females approaching menopause, a critical and understudied life stage.
Objective: To describe whole blood concentrations of toxic, essential, and trace elements in females enrolled in a 2018–2021 follow-up of the Canadian Maternal-Infant Research on Environmental Chemicals cohort, and examine differences in concentrations by sociodemographic and obstetrical history characteristics.
Methods: We analyzed whole blood samples (n = 288) for concentrations of 21 elements. For 14 elements with >50% detection, we calculated Spearman correlations and compared geometric means across strata of participant characteristics.
Results: Element concentrations were similar or lower than reported for similarly aged females in Canada. Participants seemed to have adequate concentrations of essential elements except for zinc, where most were below the proposed zinc adequacy biomonitoring equivalent (6017 μg/L whole blood). The strongest correlations (ρ = 0.41–0.63) were observed between toxic elements which may share exposure sources (mercury/arsenic), and essential elements associated with blood cell production/function (iron/cobalt/copper/zinc/manganese/selenium). Participants' geometric mean element concentrations were generally 1.1–2.0 times higher among peri-/post-menopausal participants (lead), those with unknown menopausal status (iron), older participants (cadmium), younger participants (iron, beryllium), smokers (lead, cadmium), non-smokers (selenium), lower BMI (lead, mercury, arsenic, cesium), higher BMI (manganese, copper), higher household income (nickel), and higher education (mercury, arsenic, cesium).
Conclusions: We provide important biomonitoring data for elements among adult females approaching the menopausal transition.

Abbreviations: As, Arsenic; Be, Beryllium; Cd, Cadmium; Cs, Cesium; Cr, Chromium; Co, Cobalt; CI, Confidence Interval; Cu, Copper; Ga, Gallium; GM, Geometric mean; Fe, Iron; Pb, Lead; LOD, Limit of Detection; Li, Lithium; Mn, Manganese; MIREC, Maternal-Infant Research on Environmental Chemicals study; MIREC-ENDO, Maternal-Infant Research on Environmental Chemicals - Endocrine study; Hg, Mercury; Ni, Nickel; QC, Quality control; Se, Selenium; Ag, Silver; Sr, Strontium; Tl, Thallium; U, Uranium; Va, Vanadium; Zn, Zinc; P95, 95th percentile.

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1. Introduction

Exposure to toxic elements, such as lead (Pb), cadmium (Cd), mercury (Hg), or arsenic (As), as well as deficiencies in, or excessive exposures to, essential elements (such as iron (Fe), copper (Cu), manganese (Mn), zinc (Zn), and selenium (Se)) are associated with numerous adverse health effects, including adverse reproductive health effects in females such as infertility (Henriques et al., 2019; Flora et al., 2012; Mistry et al., 2012; Tuormaa, 2000), menstrual disorders (Henriques et al., 2019; Apostoli and Catalani, 2015; Mendola et al., 2008), miscarriage (Mojadadi et al., 2021; Flora et al., 2012; Mistry et al., 2012; Tuormaa, 2000), stillbirth (Henriques et al., 2019; Apostoli and Catalani, 2015), pre-eclampsia (Borghese et al., 2023; Flora et al., 2012; Mistry et al., 2012), gestational hypertension (Borghese et al., 2023; Flora et al., 2012; Mistry et al., 2012), and preterm birth (Mojadadi et al., 2021; Henriques et al., 2019; Apostoli and Catalani, 2015; Flora et al., 2012; Mistry et al., 2012). Additionally, elevated toxic and/or elevated or deficient essential element exposures are associated with earlier onset of menopause (Tang et al., 2024; Wang et al., 2021a; White et al., 2020; Apostoli and Catalani, 2015) as well as changes in hormone concentrations (Tang et al., 2024; Zhang et al., 2023; Wang et al., 2023; Li et al., 2021) and increased risk of cardiovascular disease (Nguyen and Kim, 2022; Wang et al., 2021b; Choi et al., 2020) around the menopausal transition.

Few studies have measured both toxic and essential elements during the peri-menopausal period. Nationally representative studies, such as the Canadian Health Measures Survey (CHMS) and the U.S. National Health and Nutrition Examination Survey (NHANES), have measured concentrations of toxic elements and some essential and trace elements in general populations. However, data for several essential and trace elements, especially in whole blood are lacking. For example, several essential elements previously measured in the CHMS, such as Cu, Mn, Zn, and cobalt (Co), have not been measured since 2009–2011 (Health Canada, 2024), and some trace elements have not been measured in whole blood in either the CHMS or NHANES. Additionally, although these surveys include participants in the perimenopausal period, data on the specific sociodemographic and obstetric history characteristics relevant to this life stage (e.g., menopausal status, lifetime history of breastfeeding) are rarely collected. This is a critical reproductive life stage due to the long-term health implications of the changes that occur during the menopausal transition (Nappi et al., 2022; El Khoudary et al., 2019). For example, menopause is a risk factor for cardiovascular disease (Nappi et al., 2022; El Khoudary et al., 2019) and bone mineral density loss during menopause contributes to the development of osteoporosis (McClung et al., 2021). It is important to characterize exposure not just generally, but in this understudied, reproductive life stage in order to identify subpopulations that may be disproportionately impacted by exposure to both toxic and essential and trace elements. Our objective was to measure and describe whole blood concentrations of 21 toxic, essential, and trace elements in adult females around the age of menopause from a 2018–2021 follow-up study of the Canadian Maternal-Infant Research on Environmental Chemicals (MIREC) pregnancy cohort, the MIREC Pubertal Timing, Endocrine and Metabolic Function (MIREC-ENDO) study. The rich sociodemographic and obstetrical and reproductive history data from this longitudinal cohort provides a unique opportunity to examine concentrations of elements in a perimenopausal population.

2. Methods

2.1. Study design and participants

The MIREC pregnancy cohort recruited pregnant participants from obstetrical and prenatal clinics from 10 cities in Canada during their first trimester of pregnancy (2008–2011) (Arbuckle et al., 2013). Participants were eligible to participate if they were: >18 years of age, <14 weeks gestation, able to communicate in English or French, and planning to deliver at a local hospital. In the MIREC-ENDO follow-up study (2018–2021) a subset of the participants from 8 of the initial 10 cities completed a clinic visit in which participants provided biological samples, had physical measures taken, and completed a questionnaire to collect information on sociodemographic factors and obstetrical history (Borghese et al., 2024; Fisher et al., 2023). Both the MIREC and MIREC-ENDO studies were approved by the Research Ethics Boards of Health Canada/Public Health Agency of Canada, Sainte-Justine University Hospital, as well as the ethic boards for all MIREC-affiliated study sites. Informed consent was obtained from all participants for the MIREC-ENDO study and this analysis was restricted to those who also provided informed consent for the storage and use of their data/-biospecimens in the MIREC Biobank.

2.2. Whole blood collection and analytical methods

Whole blood samples from 288 participants that were collected and biobanked as part of the 2018–2021 follow-up MIREC-ENDO study were analyzed for concentrations of 21 elements at the Université de Montréal using Inductively-Coupled Plasma Mass Spectrometry (ICP-MS) using previously described methods (Ratelle et al., 2018, 2020). The elements measured included: silver (Ag), arsenic (As), beryllium (Be), cadmium (Cd), cesium (Cs), cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), gallium (Ga), mercury (Hg), lithium (Li), manganese (Mn), nickel (Ni), lead (Pb), selenium (Se), strontium (Sr), thallium (Tl), uranium (U), vanadium (V), and zinc (Zn). Samples were digested in four batches, and analyzed in two sets. Cs was added to the panel of metals for the second set of samples (digestion batches 3 and 4), so Cs data are only available for 161/288 samples. For each set of samples analyzed, a whole blood quality control (QC) reference sample (QM-B-Q221) from the Institut National de Santé Publique du Québec (INSPQ) was included and analyzed in triplicate. For those metals with a concentration available for the QC reference material (Pb, Cd, Hg, As, Mn, Cu, Zn, Se, Sr, Ni, Be, Co, Cr, V, Ag, U, Tl, and Cs), accuracy (calculated using the mean concentrations of the analytes in the triplicate reference samples) ranged between 82% and 104% (Supplementary Table 1). Accuracy was not calculated for Fe, Li, and Ga because concentrations were not available for these elements in the QC reference material.

2.3. Covariates

We selected covariates based on previously reported associations with one or more of the examined elements in the whole blood samples (Ates Alkan et al., 2019; Park and Choi, 2019; Wang et al., 2018; Kim et al., 2015; Adams and Newcomb, 2014; Chelchowska et al., 2013; Scinicariello et al., 2013; Padilla et al., 2010). This included: menopausal status (premenopausal, peri/post-menopausal, and unknown menopausal status), cumulative lifetime duration of breastfeeding (<12, 12–24, and >24 months), parity (1, 2, and ≥3 children), age (<40, 40–45, and >45 years), body mass index (BMI) (normal/underweight, overweight, and obese (Health Canada, 2003), derived from measured height and weight), household income (≤CAD$100,000, >$100,000), level of education (completed/some of college, trade school, and/or high school, and completed/some university), cigarette smoking status (never, former, and current), and country of birth (Canada, other). Menopausal status was self-reported. Those categorized as pre-menopausal were those reporting that they were pre-menopausal (having regular menstrual periods) or those currently pregnant. Those categorized in the peri-/post-menopausal group were those reporting they were peri-menopausal (changes in menstrual period but not having gone 12 months without one) or those reporting they were post-menopausal (over 12 months since last menstrual period). Those categorized as having an unknown menopausal status included those taking hormonal contraceptives that impact menstruation as well as those indicating their status as unknown. Additionally, due to the low

number of participants reporting their race or ethnicity as a category other than "White", we categorized participants as "White" if they exclusively identified their race or ethnicity as White and were categorized as "Other" if they selected any other category or combination of categories. We acknowledge that race or ethnicity most likely does not directly influence element concentrations but we consider these factors as proxies for unmeasured cultural or societal influences including structural/institutional racism (Williams et al., 2016, 2019) which are not fully captured by using our other covariates (such as household income, and maternal education). Weight retention was calculated by subtracting the baseline pre-pregnancy bodyweight (self-reported in MIREC, 2008–2011) from the bodyweight at follow-up (MIREC-ENDO, 2018–2021), and weight retention was categorized as a loss of any weight or a weight gain of less than 2.27 kg (<5 lbs) vs a weight gain of 2.27–6.80 kg (5–15 lbs) vs a weight gain of >6.80 kg (>15 lbs).

2.4. Statistical analysis

Statistical analyses were conducted using SAS Enterprise Guide 7.1 (SAS institute, Cary, NC) and R v. 4.2.1 (R Core Team, 2022. R Foundation for Statistical Computing, Vienna, Austria). Concentrations below the limit of detection (LOD) were substituted with one-half of the LOD to maintain comparability with other biomonitoring studies in Canada that also use this method such as the CHMS (Health Canada, 2021a). We calculated summary statistics including the minimum, median, maximum, and select percentiles (10^{th}, 25^{th}, 75^{th}, and 95^{th}) for all compounds. For those elements with a detection frequency of >50% we calculated Spearman correlations (Spearman's rho) and used general linear models with log_2-transformed element concentrations as the dependent variable to calculate geometric mean (95% CI) concentrations both overall and within strata of sociodemographic and obstetrical history characteristics. We used ANOVA to test for differences between group-specific means. When the overall group effect was statistically significant (p-value <0.05) for covariates with more than two categories we conducted pairwise comparisons using the Bonferroni method.

3. Results

The median age of participants was 42 years (range: 32–56 years). Consistent with the sociodemographic composition of the overall MIREC cohort, participants tended to self-report their race and ethnicity as White, be born in Canada, and have a high level of education and household income (Table 1). The majority of participants were never smokers (68%), had at least two children (73%), and were premenopausal (61%, n = 176, including a few (~1%) who were currently pregnant). Approximately 20% (n = 58) of participants had an unknown menopausal status, the majority of whom were using hormonal contraceptives that prevent menstruation (n = 45). The detection frequency was 100% for Pb, Cd, Mn, Fe, Cu, Zn, Se, Sr, and Cs (Table 2). Hg and As were detected in 99% and 97% of samples, respectively. Ni, Be, and Co were detected in more than 50% of samples while Cr, Ga, V, Li, Ag, and U were infrequently detected (<50%); Tl was not detected in any of the samples (Table 2). We observed moderate positive correlations (Spearman's rho 0.40–0.63) between Hg and As, Fe and Zn, Fe and Co, Pb and Cs, and Be and Co concentrations (Fig. 1). Fe and Co were moderately or weakly positively correlated with several other elements, especially essential elements, including Zn, Cu, Se, Co, Cs, and Mn, and Co for Fe, and Cd, Hg, Mn, Fe, Cu, Zn, and Be for Co.

Geometric mean concentrations of Pb were 1.3 times higher among grouped peri-/post-menopausal vs. premenopausal participants, but we did not observe significant differences in geometric Pb concentrations across age categories (Table 3, Supplemental Tables 2–3). Additionally, geometric mean concentrations of Cd and Pb were higher among current cigarette smokers (4.0 and 1.6 times higher than in never smokers, for Cd and Pb respectively), and for Cd 1.2 times higher in those who were older (40–45 vs. < 40 years of age). Finally, geometric mean concentrations were 1.3, 1.4, and 2.0 times higher for Pb, Hg, and As, respectively, among those with lower BMI (normal/underweight) compared to those with an obese BMI, and for Hg 1.4 times higher among those with a lower weight retention (any weight loss or a weight gain of < 2.27 kg) compared to those with a weight gain of > 6.80 kg.

For the essential and trace elements (Table 3, Supplemental Tables 4–8), those with an unknown menopausal status had higher geometric mean Fe concentrations (1.1 times higher) compared to those who were peri-/post-menopausal. Geometric mean concentrations were also higher among never/former smokers for Se (1.1 times higher than current smokers), those with a higher income for Ni (1.3 times higher than those with a lower income), and those with a higher level of education for Cs (1.3 times higher than those with a lower level of education). For BMI, geometric mean concentrations of elements were higher among those with a lower BMI for Cs (1.4 times higher in those with a normal/underweight BMI compared to an obese BMI), in those with a higher BMI for Mn and Cu (1.1 times higher in those with an obese BMI compared to those with a normal/underweight BMI), and among those with a higher weight retention for Cu (1.1 times higher among those with > 6.80 kg weight gain compared to those who lost weight or gained < 2.27 kg).

Table 1
Sociodemographic characteristics of adult female participants in the MIREC-ENDO study (2018–2021; n = 288).

Characteristic	n (%)
Age (years)	
<40	83 (29)
40–45	120 (41)
>45	85 (30)
Body mass index	
Normal/underweight	123 (43)
Overweight	79 (27)
Obese	57 (20)
Missing	29 (10)
Weight retention (kg)	
Weight loss (any) or a gain of <2.27	83 (29)
2.27–6.80	89 (31)
>6.80	86 (30)
Missing	30 (10)
Household income ($CAD)	
≤100,000	80 (28)
>100,000	202 (70)
Missing	6 (2)
Level of education	
Completed/some college/trade school/high school	69 (24)
Completed/some university	219 (76)
Parity	
1	33 (11)
2	121 (42)
≥3	86 (31)
Missing	48 (17)
Smoking status	
Never	195 (68)
Former	72 (25)
Current	21 (7)
Country of birth	
Canada	246 (85)
Other	36 (13)
Missing	6 (2)
Race	
White	256 (89)
Other	26 (9)
Missing	6 (2)
Menopausal status	
Pre-menopausal	176 (61)
Peri- or Post-menopausal	54 (19)
Unknown	58 (20)
Lifetime duration of breastfeeding (months)	
<12	53 (19)
12–24	67 (23)
>24	128 (44)
Missing	40 (14)

Table 2
Descriptive statistics for whole blood element concentrations in adult females from the MIREC-ENDO study (2018–2021).

Element	Units	LOD	% > LOD	Geometric mean (95% CI)	Min	Percentiles					Max
						10th	25th	50th	75th	95th	
Lead (Pb)	μg/dL	0.0042	100	0.44 (0.41, 0.47)	0.10	0.24	0.31	0.41	0.61	1.06	16.48
Cadmium (Cd)	μg/L	0.006	100	0.21 (0.19, 0.23)	0.03	0.10	0.14	0.20	0.28	0.62	3.04
Mercury (Hg)	μg/L	0.031	99	0.80 (0.72, 0.88)	<LOD	0.29	0.54	0.89	1.34	2.57	4.66
Arsenic (As)	μg/L	0.009	97	0.34 (0.29, 0.40)	<LOD	0.07	0.17	0.38	0.90	2.30	5.20
Manganese (Mn)	μg/L	0.082	100	7.54 (7.23, 7.82)	2.91	5.04	6.03	7.58	9.40	12.60	17.86
Iron (Fe)	mg/L	NA	100	382.6 (377.3, 388.0)	211.0	338.0	356.8	375.2	408.7	479.4	523.7
Copper (Cu)	μg/L	0.566	100	710.2 (695.0, 725.7)	474.8	579.3	624.0	696.9	795.0	986.1	1841
Zinc (Zn)	μg/L	2.86	100	4224 (4155, 4293)	2664	3514	3868	4310	4600	5448	6131
Selenium (Se)	μg/L	4.0	100	136.7 (134.3, 139.2)	78.92	112.4	122.6	135.9	151.0	178.3	208.4
Strontium (Sr)	μg/L	0.020	100	14.05 (13.48, 14.64)	5.24	9.27	11.37	14.12	16.97	24.04	80.53
Cesium (Cs)	μg/L	0.012	100	1.42 (1.31, 1.54)	0.29	0.79	1.11	1.40	1.96	2.96	3.97
Nickel (Ni)	μg/L	0.215	61	0.26 (0.24, 0.29)	<LOD	<LOD	<LOD	0.25	0.47	0.90	181.0
Beryllium (Be)	μg/L	0.011	61	0.03 (0.03, 0.04)	<LOD	<LOD	<LOD	0.05	0.09	0.15	0.23
Cobalt (Co)	μg/L	0.149	58	0.16 (0.15, 0.17)	<LOD	<LOD	<LOD	0.17	0.27	0.48	1.22
Chromium (Cr)	μg/L	0.021	40	–	<LOD	<LOD	<LOD	<LOD	0.10	1.07	15.08
Gallium (Ga)	μg/L	0.001	27	–	<LOD	<LOD	<LOD	<LOD	0.02	0.12	0.41
Vanadium (V)	μg/L	0.117	24	–	<LOD	<LOD	<LOD	<LOD	<LOD	0.42	1.47
Lithium (Li)	μg/L	0.087	14	–	<LOD	<LOD	<LOD	<LOD	<LOD	2.20	2379
Silver (Ag)	μg/L	0.004	6	–	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.33
Uranium (U)	μg/L	0.006	<1	–	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.02
Thallium (Tl)	μg/L	0.103	0	–	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD

LOD = Limit of detection, 95% CI = 95% Confidence interval, Min = minimum, Max = maximum.
Sample size is n = 161 for cesium, and n = 288 for all other elements.
Geometric mean was not reported for analytes if >50% of the samples were < LOD.
NA: A LOD is not applicable for iron in whole blood as iron is always present at detectable levels in whole blood.

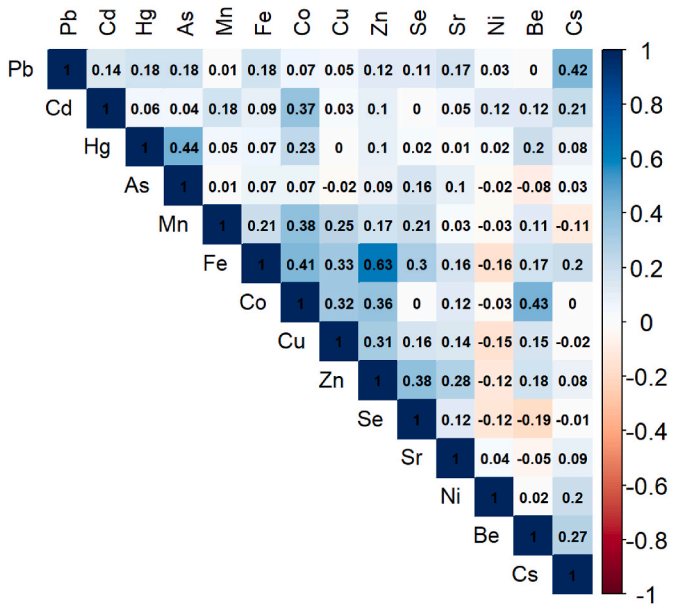

Fig. 1. Spearman's correlations between elements with >50% detection in whole blood samples from adult female participants from MIREC-ENDO (2018–2021) Negative correlations are indicated by red and positive by blue. For positive correlations, a correlation was considered strong when > 0.70, moderate from 0.40 to 0.70, weak from < 0.40 to 0.20, and very weak/negligible when < 0.20. For negative correlations, a correlation was considered strong when < -0.70, moderate from −0.40 to 0.70, weak from > -0.40 to −0.20, and very weak/negligible when > -0.20.

4. Discussion

We provide some of the first Canadian biomonitoring data for select trace elements in whole blood as well as important biomonitoring data for toxic, essential, and trace elements among adult females approaching the menopausal transition. Concentrations of several elements were positively correlated, especially essential elements associated with red blood cell production/function (such as Fe, Co, Cu, Zn, Mn, and Se). Although geometric mean concentrations of the elements were similar across factors such as lifetime duration of breastfeeding and parity, several element concentrations differed according to other characteristics such as current menopausal status, age, BMI, weight retention, household income, level of education, and cigarette smoking status. These results can be used to identify populations that may be disproportionately impacted by exposure to both toxic and essential elements.

4.1. Toxic elements: lead, cadmium, mercury, and arsenic

Whole blood concentrations of the toxic elements Pb, Cd, Hg and As were relatively low in the current MIREC-ENDO follow-up study. Geometric mean concentrations of Pb, Cd, and As were similar to or lower than those measured previously in the full MIREC cohort during the 1st trimester of pregnancy (2008–2011) (Ettinger et al., 2017; Arbuckle et al., 2016). However, the geometric mean Hg concentration (0.80 μg/L) for this study was somewhat higher than the geometric Hg concentration (0.61 μg/L) measured in the full MIREC cohort during the 1st trimester of pregnancy (2008–2011) (Arbuckle et al., 2016). Geometric mean concentrations of Pb, Cd, Hg, and As in participants in this study were also similar (i.e., Hg) to or lower (i.e., Pb, Cd, As) than those measured in the general population of Canada for females of a similar age (Fig. 2).

For the elements with biomonitoring health-based guidance values, biomonitoring equivalents, and/or reference values, the vast majority of MIREC-ENDO participants had toxic element concentrations below these values (values used and percent exceedances are included in Supplementary Table 9).

Our observation of higher geometric mean blood Pb and Cd concentrations in cigarette smokers compared to never or former smokers (Supplementary Table 2) was expected, as cigarette smoke is a predominant source of Cd and Pb exposure (Health Canada, 2021b; Adams and Newcomb, 2014; Caruso et al., 2014; Chelchowska et al., 2013; Pappas, 2011; Galażyn-Sidorczuk et al., 2008). Our finding of lower geometric mean Cd concentrations in those aged <45 years compared to those aged 40–45 years is consistent with previous reports of Cd concentrations increasing with age as a result of bioaccumulation (Kim

Table 3
Summary of differences between geometric mean toxic, essential, and trace element concentrations by covariate categories.

		Age	BMI	Post-partum weight retention	Income	Education	Smoking status	Menopausal status
Toxic elements	Lead		↓				↑	↑
	Cadmium	↑					↑	
	Mercury		↓	↓		↑		
	Arsenic		↓			↑		
Essential elements	Manganese		↑					
	Iron	↓						↑[b]
	Copper		↑	↑				
	Zinc	↓[a]						
	Selenium						↓	
	Strontium							
	Cobalt							
	Nickel				↑			
Trace elements	Beryllium	↓						
	Cesium		↓			↑		

ANOVA was used to test for differences between group-specific means. When the overall group effect was statistically significant (p-value < 0.05) for covariates with more than two categories, pairwise comparisons were conducted using the Bonferroni method. These results are presented in Supplemental Tables 2-8

↑ Indicates that geometric mean element concentrations were statistically significantly higher in a higher versus lower category of the covariate

↓ Indicates that geometric mean element concentrations were statistically significantly lower in a higher versus lower category of the covariate

Geometric mean concentrations for any element did not differ significantly by level of any of the additional covariates examined in this study (race, country of birth, breastfeeding history, country of birth

[a] Although zinc concentrations significantly differed according to the overall test, differences were not statistically significant between age categories in the pair-wise comparisons

[b] Iron concentrations were higher in the unknown menopausal status category compared to the peri-post menopausal category

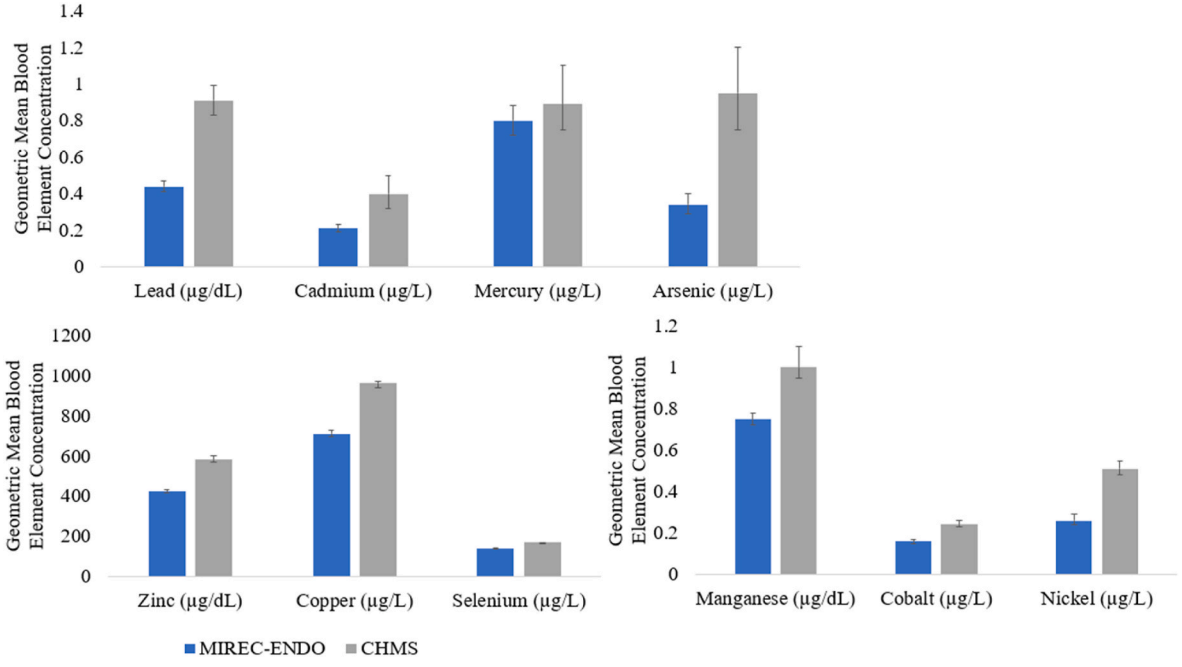

Fig. 2. Geometric mean (95% CI) concentrations of lead, cadmium, mercury, arsenic, zinc, copper, selenium, manganese, cobalt, and nickel in whole blood from adult females in MIREC-ENDO (2018–2021) compared to concentrations from adult female participants aged 40–59 years in the Canadian Health Measures Survey.

et al., 2015; Adams and Newcomb, 2014). Similarly, the inverse relationship between Pb concentrations and BMI is consistent with previous findings for this cohort during pregnancy (2008–2011) (Arbuckle et al., 2016), and consistent with findings from some other studies (Scinicariello et al., 2013; Padilla et al., 2010), but not all (Park and Choi, 2019; Wang et al., 2015, 2018; Ronco et al., 2010; Hauser et al., 2008).

The higher observed geometric mean blood Pb concentrations in participants that identified as peri-/post-menopausal may be due to increased bone mineral resorption/bone demineralization in menopause

(Khosla et al., 2012; Nash et al., 2004; Väänänen and Härkönen, 1996) as a result of reduced estrogen concentrations (Heshmati et al., 2002). Several studies have detected higher blood Pb concentrations in post-menopausal participants (Nash et al., 2004; Garrido Latorre et al., 2003; Hernandez-Avila et al., 2000; Symanski & Hertz-Picciotto, 1995). Although Pb concentrations in blood can also increase with age (Ettinger et al., 2020), geometric mean Pb concentrations were not statistically significantly different across the age categories in this study, but did show a slight increasing trend across the age categories. In a previous analysis, Pb concentrations were higher during pregnancy in those over 35 years of age in the full MIREC cohort (2008–2011) (Arbuckle et al., 2016). Geometric mean Pb concentrations tended to be higher among participants born outside of Canada and among those whose self-identified race or ethnicity was other than "White", though the small sample sizes of the participants in these categories may explain the wide confidence intervals around these estimates (and also for the other elements). These results are consistent with other studies finding differences in Pb concentrations by race or ethnicity and country of birth (Ettinger et al., 2020; Bulka et al., 2019), and findings from the full MIREC cohort for Pb concentrations during pregnancy (Arbuckle et al., 2016).

The CHMS data for lead, cadmium, mercury, and selenium were from 2018 to 2019, while the CHMS data for zinc, copper, manganese, cobalt, and nickel were from 2009 to 2011, and the CHMS data for arsenic were from 2007 to 2009 (Health Canada, 2024). Units were converted as needed to facilitate comparison with other elements on a single axis.

The observed moderate positive correlation between Hg and As, along with the similar patterns of differences across sociodemographic factors, is likely due to a common source of exposure, such as the consumption of fish and seafood (Singh et al., 2023; Health Canada, 2019; Awata et al., 2017; Taylor et al., 2017; Bae et al., 2017; Molin et al., 2015; Miklavčič et al., 2013; Park and Lee, 2013; Navas-Acien et al., 2011; Rivera-Núñez et al., 2012). The higher concentrations of Hg and As among those with lower BMI and higher level of education may be explained by associations with diet quality, which is associated with greater fish consumption (Bocquier et al., 2015; Gil et al., 2015), lower BMI (Asghari et al., 2017; Nicklas et al., 2012; Wolongevicz et al., 2010), and higher levels of education (Asghari et al., 2017; Hiza et al., 2013). This may also explain the weak correlations observed between whole blood Hg concentrations and other elements, such as Co, as fish and seafood are also dietary sources of Co (in the form of vitamin B12) (Genchi et al., 2023).

4.2. *Essential elements: iron, zinc, copper, selenium, manganese, cobalt, and nickel*

Geometric mean concentrations of essential elements (Zn, Cu, Se, Mn, Co, and Ni) in the current study of adult female participants tended to be lower than observed in the general population of Canada (Health Canada, 2024) (Fig. 2). Geometric mean manganese concentrations were also lower than those previously measured in the full MIREC cohort during pregnancy (Arbuckle et al., 2016). For some of these essential elements, biomonitoring equivalents have also been established for adequacy and/or to avoid excessive exposures (Supplementary Table 9). The geometric mean and 10th percentile of selenium concentrations in this study were above the biomonitoring equivalent for adequate Se intake, and the 95th percentile and maximum measured selenium concentration was below the biomonitoring equivalent for excessive Se concentrations. The geometric mean, 95th percentile, and all but one (the maximum) of the zinc concentrations measured in the current study fell below the biomonitoring equivalent of 6017 μg/L in whole blood indicating inadequate Zn concentrations for women (Poddalgoda et al., 2019). Low/inadequate Zn intakes and concentrations have been previously reported in the general population of Canada (Ahmed et al., 2021; Health Canada, 2012). Zn is an essential element required for the function of over 300 enzymes that are involved in a wide range of essential functions (Chasapis et al., 2012, 2020) and Zn deficiency has been associated with numerous adverse health effects, including on the skeletal and immune system, and is associated with increased risk of cardiovascular and metabolic disease (Chasapis et al., 2020). It should be noted that due to homeostasis in blood, urinary zinc may be a more reliable biomarker of Zn exposure than blood measures (whole blood, serum, plasma) (Poddalgoda et al., 2019). However, the relatively low concentrations of Zn measured in whole blood in this study, which are below blood concentrations corresponding with a biomonitoring equivalent for adequate intake levels, raises concerns for whether there may be inadequate Zn intakes for optimal health, or even Zn deficiencies, in this subpopulation, and other subpopulations in Canada. Biomonitoring equivalents have not yet been established for Cu, Mn, Co, and Ni. The geometric mean, 95th percentile, and maximum Co concentrations measured in the MIREC-ENDO participants in this study were well below blood concentrations of Co associated with negative health effects in human studies (such as 26 μg/L for cardiomyopathy in heavy beer drinkers) (Environment and Climate Change Canada, Health Canada, 2017).

Fe concentrations are not typically reported for whole blood and are not used to identify Fe deficiencies; rather, measures such as haemoglobin, serum ferritin, transferrin saturation, and serum soluble transferrin receptor are used to provide information on individuals' Fe status (Lopez et al., 2016). Nevertheless, the availability of whole blood Fe concentrations allowed us to examine whether concentrations of Fe were correlated with concentrations of other elements measured in this study that are also important for red blood cell production and function. As expected, Fe and Co concentrations were moderately correlated, as Co is part of the essential nutrient vitamin B12, which is required for the production of red blood cells (Finley et al., 2012; Langan and Goodbred, 2017). Co and Fe had the most numerous moderate and weak positive correlations with the other elements measured in these blood samples, and many of these associations were with other elements also involved in red blood cell production and/or function such as Zn, Mn, Cu, and Se (Takahashi, 2022; Liao et al., 2018; Wessling-Resnick, 2017). The geometric mean concentration of Fe in whole blood in this study was similar to or lower than Fe concentrations measured in adult females in the limited studies reporting Fe concentrations in whole blood (Aziz et al., 2015). The finding of lower geometric mean Fe concentrations in those $>$ 45 years of age (compared to those $<$ 40), and higher geometric mean Fe concentrations in those with an unknown menopausal status (compared to those who were pre-menopausal or peri-/post-menopausal) were not unexpected. Higher Fe whole blood concentrations in those with an unknown menstrual status is likely due to reduced Fe loss due to decreased menstruation with the use of contraceptives/birth control that reduce and/or prevent menstruation, as has been previously reported for markers of Fe status (e.g., serum ferritin and hemoglobin) (Chang et al., 2023; Spencer et al., 2019; Miller, 2014; Milman et al., 1992).

Several of the other essential elements measured in this study also differed by participant sociodemographic characteristics. Geometric mean Mn and Cu concentrations were higher in those with an obese BMI compared to those with a normal/underweight BMI. A 2020 meta-analysis by Gu et al. (2020) found that higher serum Cu concentrations may be associated with risk of obesity in adults and additional recently published studies have also found associations between serum copper concentrations and BMI/adiposity measures (Liu et al., 2024; Soto-Sánchez et al., 2023; Wu et al., 2023). However, for Mn results have not been consistent, with both positive, null, and negative associations observed between Mn exposure and BMI/obesity/other markers of adiposity and/or metabolic disease in different populations as described in a review by Li and Yang (2018). Further research is needed to clarify the associations between these elements and obesity in adults. The finding of lower geometric mean Se concentrations in current cigarette smokers compared to never or former smokers is consistent with the literature for several different populations (Ates Alkan et al.,

2019; Jain and Choi, 2015; Batáriová et al., 2005; Luty-Frąckiewicz et al., 2002; Kocyigit et al., 2001). The higher geometric mean blood Ni concentrations observed in those with a higher household income, may be due to differences in diet, since diet is the main source of Ni exposure for the general population (Health Canada, 2013).

4.3. Trace elements: lithium, beryllium, vanadium, chromium, gallium, strontium, silver, thallium, uranium, and cesium

This analysis provides important information for several trace elements in whole blood that are not commonly measured (Ag, Cr, Li), or to the best of our knowledge have not been measured and/or published (Be, Va, Cr, Ga, Sr, Ag, Tl, U, Cs) to date in the general population of Canada. Concentrations of Sr, Cs, and Be in MIREC-ENDO participants tended to be, on average, lower than concentrations in whole blood samples from Indigenous communities in northern Canada through the Old Crow, Yukon (Drysdale et al., 2021) and Mackenzie River Valley, Northwest Territories (NWT) (Ratelle et al., 2018, 2020) biomonitoring projects (Fig. 3, Supplemental Table 10). Although these northern Canadian biomonitoring projects used the same analytical method and laboratory as was used for this study of MIREC-ENDO participants, the populations in these studies have notably different sociodemographic characteristics, lifestyles, and exposure sources (including diet) (AMAP, 2021). They are being used for comparison in this case due to a lack of other Canadian or North American data for comparison.

Be concentrations were very low and close to the LOD for this study, similar to previous biomonitoring studies in northern Canada (Drysdale et al., 2021; Ratelle et al., 2018, 2020). A review of Be biomonitoring data from North America (Health Canada, 2016) found the vast majority of Be values were < LOD in the studies examined, including in whole blood samples from Quebec, Canada (although the LOD in that study, 0.45 μg/L, was much higher than in this study), with the exception of one cycle of NHANES (NHANES-III, 1988–1994) which saw a 67% detection in urine. However, in some more recent studies with similar LODs to this study (ranging between 0.004 and 0.020 μg/L), detection frequencies for Be in whole blood have been higher (ranging between 44%–57%) and detection frequencies and 95th percentiles (where reported) seemed to be similar to those reported in this study (Syversen et al., 2021; Nisse et al., 2017).

Detection frequencies and concentrations of the elements Cr, Ga, V, Li, Ag, U, and Tl in whole blood were low in the current study, which is similar to previous results from biomonitoring projects in northern Canada (Supplementary Table 10). Ag concentrations in the MIREC-ENDO participants were below the LOD for the majority of samples, lower than those reported from the CHMS (Health Canada, 2024), and the geometric mean, 95th percentile, and maximum were below the biomonitoring equivalent of 0.4 μg/L (Aylward et al., 2016). Geometric mean Li concentrations were lower, but 95th percentile Li concentrations were higher in this study, compared to concentrations measured in CHMS samples from 2009 to 2011 (Jayawardene et al., 2021) and geometric mean and 95th percentile, but not the maximum, blood Li concentrations measured in this study were below proposed biomonitoring equivalents for excessive intakes (Ramoju et al., 2020). One elevated Li concentration (the maximum) in this study was relatively high but may be the result of therapeutic use (Malhi et al., 2013), as it is within the upper end of the therapeutic range (ICH, 2022), although Li containing medication use could not be confirmed for this participant. Cr concentrations could not be compared to those measured in the CHMS in 2009–2011 as a higher LOD was used in the CHMS study and all CHMS samples were below detection (Jayawardene et al., 2021).

The observed correlation among Cs, Pb, and Cd in our study is consistent with previous reports of positive correlations between concentrations of Cs and Pb in urine (Zhang et al., 2023; Christensen et al., 2013; Padilla et al., 2010), and Cs and Cd in urine (Zhang et al., 2023; Padilla et al., 2010). Similar to our findings for Pb, geometric mean Cs concentrations were also lower in those with an obese BMI compared to those with a normal/underweight or overweight BMI. Negative associations between urinary Cs concentrations and BMI have been observed in the general American population (Padilla et al., 2010) and in pregnant women from Western Australia (Hinwood et al., 2015). Similarly, our finding of higher geometric mean blood Cs concentrations in those with a higher level of education, was consistent with the findings of Geller et al. (2022) in their sample of reproductive-aged Black women in Michigan, USA, although they did not observe a significant association between blood Cs concentrations and BMI (Geller et al., 2022). Although lower geometric mean Be concentrations were observed in this study in those over the age of 45 (compared to the other age groups); this should be interpreted with caution as blood Be concentrations measured in the MIREC-ENDO participants were very low and close to the LOD. In a previous study in France, blood Be concentrations were not found to differ by age category, although their age categories were much wider than those in this study, and they also reported low blood Be concentrations (Nisse et al., 2017). Finally, the weak correlation observed between whole blood Sr and Zn concentrations (Spearman's rho = 0.28) is consistent with the weak positive correlation (Spearman's rho = 0.16) observed between whole blood Sr and Zn concentrations in communities living near the Brazilian Amazon although this population had relatively higher levels of exposure to these and other elements (Rodrigues et al.,

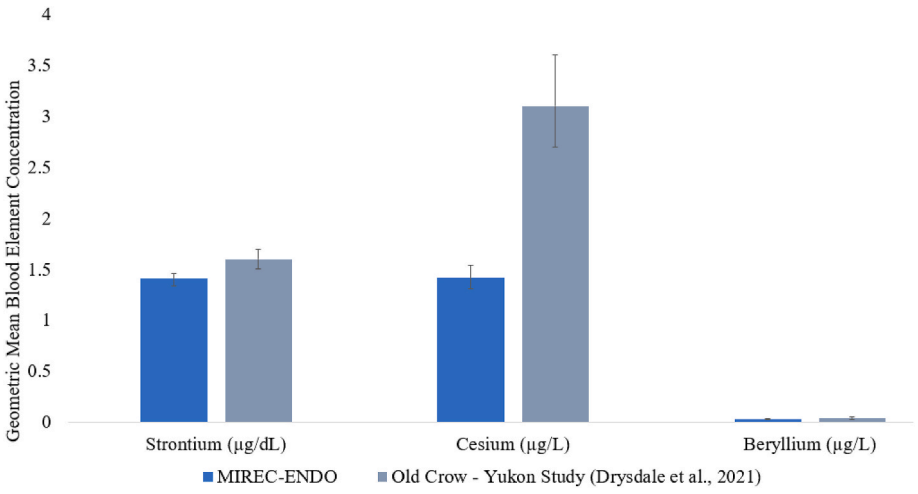

Fig. 3. Geometric mean (95% CI) concentrations of strontium, cesium, and beryllium in whole blood from adult females in MIREC-ENDO (2018–2021, n = 288) compared to concentrations from participants of the Old Crow, Yukon, Canada biomonitoring project (2019, n = 54) (Drysdale et al., 2021).

2009).

4.4. Strengths, limitations, and future directions

A strength of this study is that we present biomonitoring data for element concentrations at an understudied life stage, including several trace elements that have not previously been reported in whole blood samples from the general population of Canada. These findings may inform risk assessments of these elements. Although this analysis was cross-sectional in nature, it is embedded in a longitudinal cohort, allowing us to draw on previous data to derive sociodemographic and/or obstetric history variables that may not be possible in other studies or may require long term recall and be subject to recall bias. For example, this study design allowed us to examine variables such as changes in body weight (over approximately 10 years) and lifetime duration of breastfeeding. Despite these strengths, the sample size in our study was relatively small, and the majority of participants tended to be of a relatively high socio-economic status, White, and born in Canada. Therefore, the findings of this study may not be generalizable to all of the Canadian population. Although concentrations of some elements seemed to differ by race/ethnicity, and country of birth, these differences were not statistically significant, potentially due to the small number of participants in sub-groups. Further work is needed to determine if other Canadian subpopulations may be disproportionately impacted by exposure to these elements. Finally, while whole blood is a widely used matrix for human biomonitoring of several elements, it may not be the best matrix for assessing low-level exposure to some essential elements, especially those under homeostatic control (Cu, Fe, Mn, Zn) in the general population. Future studies could consider analyzing element concentrations in multiple matrices.

5. Conclusion

Whole blood concentrations of toxic, essential, and trace elements measured in the whole blood of female participants around the age of menopause from the Canadian MIREC-ENDO study were relatively low and were similar to, or lower than, those reported for the general population of Canada or from northern Canada. Pb concentrations were 1.3 times higher in those who were peri-/post-menopausal, consistent with previous studies, which is concerning because of the negative health effects associated with Pb exposure. Geometric mean and 95th percentile whole blood Zn concentrations fell below a proposed biomonitoring equivalent for adequate Zn intakes in whole blood for participants of this study, which could indicate widespread Zn deficiency among this, and perhaps other, subpopulations in Canada; this finding will need to be corroborated with further biomonitoring data, including urinary zinc measures, and dietary intake nutritional analyses. These findings may help guide future research investigating associations between concentrations of toxic, essential, and trace elements and health outcomes around the menopausal transition, a critical and understudied reproductive life stage.

CRediT authorship contribution statement

Sara Packull-McCormick: Writing – original draft, Visualization, Formal analysis. **Jillian Ashley-Martin:** Writing – review & editing, Project administration, Conceptualization. **Michèle Bouchard:** Writing – review & editing, Methodology, Investigation. **Mandy Fisher:** Writing – review & editing, Project administration. **Tye E. Arbuckle:** Writing – review & editing, Project administration, Formal analysis. **Kristin Macey:** Writing – review & editing. **Maryse Bouchard:** Writing – review & editing. **Warren Foster:** Writing – review & editing. **Michael M. Borghese:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

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Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2025.122095.

Data availability

The data that have been used are confidential.

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