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Trace elements in whole blood in the general population in Trøndelag County, Norway: The HUNT3 Survey

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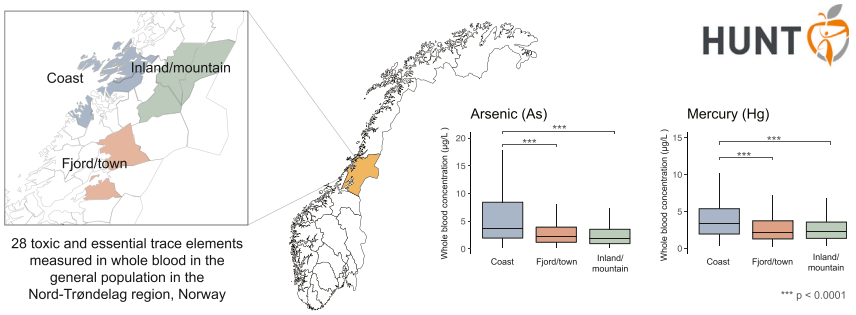
HIGHLIGHTS

- 28 trace elements were measured in whole blood (n = 1011) in a population-based study.
- Geographical area, age, and sex are associated to trace element status.
- The marine environment might be a source of exposure for As, Hg, Se and Br.
- Our study highlights how trace element levels varies in the general population.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Biomonitoring of a cohort within a large health survey can provide reliable information on trace element status. The main aims of this study were 1) to determine the concentrations of 28 trace elements in whole blood samples from the general population of the Nord-Trøndelag region, Norway, and 2) to investigate how trace element concentrations vary with geographical area, lifestyle, and socio-demographic factors.
Methods: Whole blood samples were collected in the third survey of the Trøndelag Health Survey (HUNT3), a large population-based study in Norway. In total, 1011 whole blood samples from individuals aged 20–91 years were analyzed using high resolution inductively coupled plasma-mass spectrometry (HR-ICP-MS). We compared trace element concentrations (As, B, Be, Br, Ca, Cd, Cr, Cs, Cu, Ga, Au, In, Fe, Pb, Hg, Tl, Mg, Mn, Mo, Ni, Rb, Sc, Se, Ag, Sr, Sn, W and Zn) between three geographical areas (coastal, fjord/town, inland/mountain) using multivariable linear regression and assessed differences in trace element concentrations with socio-demographic and lifestyle factors using general linear models.
Results: Trace element concentrations were generally comparable to levels reported in other recent studies and suggest low exposure to toxic trace elements in the region. We found geographical differences in concentrations of 19 trace elements. As, Br, Hg, and Se concentrations were higher on the coast compared to the fjord/town and inland/mountain areas, suggesting that the marine environment is an important source of exposure for these

Abbreviation list: AM, arithmetic mean; BMI, body mass index; CI, confidence interval; GM, geometric mean; HR-ICP-MS, high resolution inductively coupled plasma-mass spectrometry; HUNT, Trøndelag Health Study; IQR, interquartile range; SD, standard deviation.

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trace elements. In addition, socio-demographic and lifestyle characteristics, particularly age and sex, were associated with differences in trace element concentrations.

Conclusions: We report concentrations of 28 trace elements in the general population of a rural region with low exposure to pollution. Whole blood concentrations of trace elements varied with geographical area, the participants' lifestyle, and socio-demographic characteristics, highlighting the importance of considering these factors when evaluating trace element status in a population.

1. Introduction

Humans are exposed to trace elements from many sources, and for non-occupationally exposed individuals the major sources are food, water and air (Elder et al., 2015). Many trace elements are essential, important for growth and development, and have various biological functions, while others are classified as non-essential or toxic. However, essential trace elements may also be toxic depending on dose, and in addition, the essentiality of some trace elements is debated (Nielsen, 2014).

Biomonitoring is an important tool to gain information about exposures to essential and non-essential trace elements, and may provide a baseline for future surveys and help elucidate causes of diseases (Gil and Hernández, 2015). Additionally, several diseases have been linked to either trace element imbalances and deficiencies, or to exposure to toxic trace elements (Nordberg et al., 2015). A better understanding of how trace element concentrations vary with lifestyle and socio-demographic characteristics might provide a tool to identify subgroups of the population with an increased risk of trace element imbalances or deficiencies, and potentially associated diseases. Trace element concentrations in humans have been reported in numerous countries (Alimonti et al., 2011; Baeyens et al., 2014; Bárány et al., 2002; Goullé et al., 2005; Heitland and Köster, 2006; Nisse et al., 2017; Saravanabhavan et al., 2017; Snoj Tratnik et al., 2019; Wennberg et al., 2017; Yedomon et al., 2017; Zhang et al., 2015), including Norway (Averina et al., 2020; Birgisdottir et al., 2013; Caspersen et al., 2019; Fløtre et al., 2017; Meltzer et al., 2016), Table 1. However, most previous studies only report concentrations for a limited number of trace elements, in cohorts with moderate sample sizes or in segments of the population which may not be representative for the general population. In a recent study from our group (Syversen et al., 2021), we reported trace element concentrations in a cohort from the HUNT3 Survey. This cohort consisted of adults aged 50–65 years, thus not representative of the general population. The main aims of the current study were to determine 28 trace elements in the general population and to identify how trace element status varies with geographical area, lifestyle and socio-demographic factors. Whole blood samples were collected, and by applying a sex-, age-, and area-stratified probability sampling design, we selected a subset of the cohort, highly representative of the general population of the Nord-Trøndelag region, Norway. This region is predominantly rural, with low levels of industrial pollution (Langhammer et al., 2000). Samples were analyzed using high-resolution inductively coupled plasma mass spectrometry (HR-ICP-MS), paying strict attention to contamination control in all steps. By using the detailed information available through the HUNT Study, and an in-depth statistical evaluation, we highlight geographical area, lifestyle, and selected socio-demographic factors as potential determinants of trace element status in the general population.

2. Materials and methods

2.1. Study population

Non-fasting whole blood samples for trace element analysis were collected between November 2006 and November 2007 as part of the third survey of the Trøndelag Health Study (HUNT3). The HUNT Study is a large longitudinal population-based health study conducted since 1984 in the Nord-Trøndelag region, situated in the central part of Norway (Fig. 1). In HUNT, all inhabitants aged ≥20 years have been invited to participate in four consecutive cross-sectional surveys: HUNT1 (1984–86), HUNT2 (1995–97), HUNT3 (2006–08) and HUNT4 (2017–19) (HUNT Research Center, 2017), and 50,807 adults (54.1% attendance rate) participated in the HUNT3 Survey (Krokstad et al., 2013). Data has been gathered through questionnaires, interviews, clinical examinations and collection of blood and urine samples (Krokstad et al., 2013).

We selected participants from three geographical areas (coast, fjord/town, inland/mountain, Fig. 1). Specifically, five municipalities with coastline towards the Norwegian Sea (Nærøy, Vikna, Flatanger, Leka and Fosnes) were classified as 'coast', while two municipalities (Levanger and Steinkjer), each with a medium sized town (Levanger with 10,333 inhabitants and Steinkjer with 12,976 inhabitants (Statistics Norway, 2021)), situated along the Trondheim Fjord were classified as 'fjord/town'. Three municipalities (Røyrvik, Namsskogan and Grong) have no coastline and were categorized as 'inland/mountain' municipalities. We applied an sex-, age-, and area-stratified probability sampling design, and randomly selected equal numbers of men and women from the three geographical areas and the six 10-years age categories. Of the 16,808 individuals who met the eligibility criteria (age ≥ 20, living in the selected municipalities, and being non-pregnant), 1016 participants (6.0%) were selected. Individuals living in the inland/mountain and coastal areas, and those aged 20–39 and ≥70 were over-sampled due to their smaller proportion of the population. Five individuals were excluded due to low blood volume or missing samples. In total, 1011 subjects, 505 women and 506 men, were included in the study.

Residential information, age, and sex were obtained through information from the National Population Register, while information regarding i) smoking status, alcohol intake, fatty fish consumption and ii) current pregnancy status was obtained through questionnaires and interviews, respectively. Participants' height, weight, and waist circumference were measured with standardized methods at the health examination sites. We obtained data on education level and income (specifically, household after-tax income corrected for differences in household size and household composition) from Statistics Norway.

2.2. Blood sample collection and storage

Whole blood samples were collected at the health examination stations and transported daily by courier to a state-of-the art biobank at Levanger Hospital. Blood sampling followed a strict quality protocol (Krokstad et al., 2013). Five blood samples were collected from each participant using needles for routine blood collection (Vacuette, Greiner Bio-One North America, Inc., Monroe, NC, USA). To minimize the potential contamination of trace elements originating from the stainless-steel needles, samples for trace element analysis were collected as the last of the five vacutainer tubes, in a glass "trace element free" tube containing sodium heparin (Vacutainer, Becton, Dickinson & Co, Cat. no. 367735, Franklin Lakes, NJ, USA). Each trace element blood sample was further divided into seven 0.8 mL aliquots and transferred into 1 mL

Table 1
Comparison of trace element whole blood concentrations found in the present study with data from selected recent multi-element surveys.
GM – Geometric mean; P (5th, 10th, 25th, 75th and 95th): 5th, 10th, 25th, 75th and 95th percentiles; RV95: Reference values at the 95th percentile; f: females; m: males.

Element	Present study (HUNT3) (n = 1011)	Germany (Heitland and Köster, 2006) (n = 130)	Benin (Yedomon et al., 2017) (n = 70)	Canada CHMS (Saravanabhavan et al., 2017)	Norway (Birgisdottir et al., 2013) (n = 184)	China (Zhang et al., 2015) (n = 648)	Italy PROBE (Alimonti et al., 2011) (n = 1423)	Sweden (Bárány et al., 2002) (n = 243–343, adolescents)	France (Goullé et al., 2005) n = 100	France IMEPOGE (Nisse et al., 2017) (n = 1992)
	GM P(5th–95th)	GM P(5th–95th)	GM P(5th–95th)	RV95 (n)	Median P(5th–95th)	GM P(25th–75th)	GM P(5th–95th)	Median (Range)	Median P(5th–95th)	GM P(10th-95th)
Arsenic (μg/L)	2.64 (0.61–14.50)	0.71 (0.16–2.3)	5.810 (3.520–10.550)	2.0 (n = 996)	5.9 (0.8–41.0)		1.14 (0.28–5.32)		5.0 (2.6–1.8)	1.67 (0.50–6.72)
Beryllium (μg/L)	<0.0096 (<0.0096–0.0122)	<0.008 (<0.008–0.015)	0.020 (<0.010–0.196)				0.085 (<0.045–0.156)		0.02 (0.02–0.09)	0.003 (<LOD–0.09)
Boron (μg/L)	27.2 (13.1–55.2)	36 (14–41)	–	–		–	–	–	26 (14–44)	
Cadmium (μg/L)	0.36 (0.11–1.87)	0.38 (0.12–1.9)	0.319 (0.150–0.630)	0.83 (n = 2507)	0.45 (0.11–1.8)	0.68 (0.42–1.14)	0.53 (0.23–1.42)	<0.2 (<0.2–2.6)	0.31 (0.15–2.04)	0.39 (0.17–1.67)
Cesium (μg/L)	4.44 (2.66–7.43)	3.4 (2–5.5)	–	–		–	–	–		
Chromium (μg/L)	0.58 (<0.40–2.26)		<0.240 (<0.240–0.990)				0.24 (0.06–1.09)			0.42 (0.10–1.26)
Copper (mg/L)	1.01 (0.82–1.27)	1.02 (0.80–1.62)	0.870 (0.720–1.027)	1.30 (f = 3124) 1.00 (m = 2940)		0.802 (0.685–0.885)		0.92 (0.61–1.9)		
Gallium (μg/L)	0.073 (0.046–0.112)	<0.2 (<0.2–<0.2)	–	–		–	–	–	3.5 (2.65–4.71)	
Gold (μg/L)	0.0097 (<0.0057–0.0392)	0.02 (<0.012–0.45)	–	–		–	–	–		
Indium (μg/L)	0.029 (0.016–0.060)	<0.009 (<0.009–0.014)	–	–		–	–	–		
Iron (mg/L)	541 (468–631)		469 (387–554)	–		–	–	–		
Lead (μg/L)	18.8 (8.9–45.5)	19 (8–47)	47.39 (29.37–74.78)	33 (n = 3142)	24.5 (8.6–65.1)	42.55 (31.31–59.89)	19.9 (7.38–51.7)	16 (3.5–170)	26 (11.4–62.8)	18.8 (8.86–49.3)
Magnesium (mg/L)	39.6 (33.9–45.9)		27.7 (23.4–34.1)							
Manganese (μg/L)	9.11 (5.81–14.92)	8.6 (5.7–14.6)	19.71 (15.70–25.14)	16 (f = 1937) 14 (m = 1676)		11.42 (8.81–14.72)	8.19 (4.41–12.8)		7.6 (5.0–12.8)	7.71 (5.26–12.9)
Mercury (μg/L)	2.74 (0.84–9.69)	0.9 (0.2–3.3)	3.12 (1.11–7.64)	2.3 (n = 1229)	4.0 (1.2–12.6)		1.19 (0.35–5.16)	1.1 (<0.7–6.1)	3.0 (0.94–8.3)	1.38 (0.49–5.06)
Molybdenum (μg/L)	0.83 (0.44–1.78)	0.33 (0.14–1.1)	0.912 (0.370–3.160)	1.6 (n = 1759)			1.21 (0.69–2.05)		2.9 (0.77–7.86)	
Nickel (μg/L)	0.50 (<0.22–1.72)	0.08 (0.03–0.22)	–	1.1 (n = 5924)			0.89 (<0.35–2.62)		2.1 (0.09–4.18)	1.31 (0.74–2.67)
Rubidium (μg/L)	2220 (1715–2877)	2369 (1768–3131)	–					2800 (1500–4400)	1680 (1289–2358)	
Selenium (μg/L)	100.2 (75.4–136.9)	132 (105–164)	163.0 (123.0–205.0)	240 (n = 3598)	95 (63–153)			110 (55–180)	119 (89–154)	
Silver (μg/L)	<0.039 (<0.039–0.424)	0.04 (0.009–0.236)	–						1.4 (0.69–4.51)	
Strontium (μg/L)	18.0 (12.2–29.4)	19 (11–39)	30.53 (21.17–48.42)						16 (9–41)	
Thallium (μg/L)	0.026 (0.016–0.047)	0.016 (<0.01–0.035)	0.123 (0.050–0.270)				0.037 (0.018–0.098)	<0.06 (<0.06–0.15)	0.02 (0.011–0.035)	0.02 (0.01–0.14)
Tin (μg/L)	0.24 (<0.10–3.13)	0.12 (0.03–0.55)	0.211 (<0.100–0.480)				0.539 (0.124–2.250)		1.1 (0.11–1.75)	
Tungsten (μg/L)	<0.022 (<0.022–0.055)	<0.011 (<0.011–0.017)	<0.002 (<0.002–0.143)				0.028 (0.011–0.075)	<0.1 (<0.1–0.94)	0.006 (0.004–0.0822)	
Zinc (mg/L)	7.5 (5.9–9.1)		4.85 (3.68–6.67)	6.7 (f = 947) 0.9 (m = 821)		4.67 (3.78–5.56)		6.1 (3.1–9.8)		5.81 (4.77–7.27)

Element	Present study (HUNT3) (n = 1011)	Norway (Averina et al., 2020) (n = 352)	Norway (Syversen et al., 2021) (n = 757)	Norway (Caspersen et al., 2019) (n = 2982)	Norway (Fløtre et al., 2017) (n = 158)	Norway (Meltzer et al., 2016) (n = 267)	Slovenia (Snoj Tratnik et al., 2019) (n = 1084)	Sweden (Wennberg et al., 2017) (n = 1545)
	GM P(5th–95th)	Median (range)	Median (10th–90th)	GM P(5th–95th)	GM P(5th–95th)	Mean P(5th–95th)	GM P(5th–95th)	Median P(25th, 75th)
Arsenic (μg/L)	2.64 (0.61–14.50)		2.88 (0.89–8.84)	1.3 (0.24–7.0)		3.2 (0-9.3)	0.89 (0.35–3.74)	
Beryllium (μg/L)	<0.0096 (<0.0096–0.0122)		<0.020 (<0.020–0.088)					
Boron (μg/L)	27.2 (13.1–55.2)		25.6 (6.8–46.9)					
Cadmium (μg/L)	0.36 (0.11–1.87)	0.26 (<0.11–3.89)	0.36 (0.15–1.21)	0.16 (0.07–0.46)	0.17 (0.08 -0.87)		0.28 (<LOD–1.01)	0.12 (0.09-0.17) (m = 152) 0.16 (0.12-0.24) (f = 325)

(continued on next page)

Table 1 (*continued*)

Element	Present study (HUNT3) (n = 1011)	Norway (Averina et al., 2020) (n = 352)	Norway (Syversen et al., 2021) (n = 757)	Norway (Caspersen et al., 2019) (n = 2982)	Norway (Fløtre et al., 2017) (n = 158)	Norway (Meltzer et al., 2016) (n = 267)	Slovenia (Snoj Tratnik et al., 2019) (n = 1084)	Sweden (Wennberg et al., 2017) (n = 1545)
	GM P(5th–95th)	Median (range)	Median (10th–90th)	GM P(5th–95th)	GM P(5th–95th)	Mean P(5th–95th)	GM P(5th–95th)	Median P(25th, 75th)
Cesium (μg/L)	4.44 (2.66–7.43)		5.03 (3.63–7.23)					
Chromium (μg/L)	0.58 (<0.40–2.26)							
Copper (mg/L)	1.01 (0.82–1.27)		1.01 (0.87–1.37)	1.54 (1.20–1.97)		0.91 (0.65-1.17)	0.95 (0.74–1.26)	
Gallium (μg/L)	0.073 (0.046–0.112)							
Gold (μg/L)	0.0097 (<0.0057–0.0392)							
Indium (μg/L)	0.029 (0.016–0.060)		0.082 (0.033–0.154)					
Iron (mg/L)	541 (468–631)							
Lead (μg/L)	18.8 (8.9–45.5)	11.4 (<3.32-121.42)	21.1 (12.59–37.08)	8.2 (4.4–16)	8.29 (4.14 -22-79)		18.0 (9.13–41.5)	11.0 (8.94-0.15.6) (m = 152) 9.65 (7.31-12.8) (f = 325)
Magnesium (mg/L)	39.6 (33.9–45.9)							
Manganese (μg/L)	9.11 (5.81–14.92)		9.62 (6.07–13.77)	10.3 (6.1–18.0)		10.6 (2.7- 18.5)	13.8 (8.18–26.2)	
Mercury (μg/L)	2.74 (0.84–9.69)	1.9 (<0.39-25.88)	2.75 (1.35–6.51)	0.93 (0.24–2.8)	0.98 (0-3.88)		1.18 (0.30–4.78)	
Molybdenum (μg/L)	0.83 (0.44–1.78)			0.65 (0.34–1.50)				
Nickel (μg/L)	0.50 (<0.22–1.72)		0.52 (<0.15–1.63)					
Rubidium (μg/L)	2220 (1715–2877)							
Selenium (μg/L)	100.2 (75.4–136.9)		112.7 (90.5–145.1)	103 (74-144)			105 (74.2–152)	
Silver (μg/L)	<0.039 (<0.039–0.424)							
Strontium (μg/L)	18.0 (12.2–29.4)							
Thallium (μg/L)	0.026 (0.016–0.047)			0.02 (0.02–0.03)				
Tin (μg/L)	0.24 (<0.10 - 3.13)		<0.040 (<0.040–0.501)					
Tungsten (μg/L)	<0.022 (<0.022 - 0.055)							
Zinc (mg/L)	7.5 (5.9 - 9.1)		7.6 (6.3–10.8)	4.7 (3.4–6.2)		6.4 (5.0-7.8)	6.6 (5.2–8.3)	

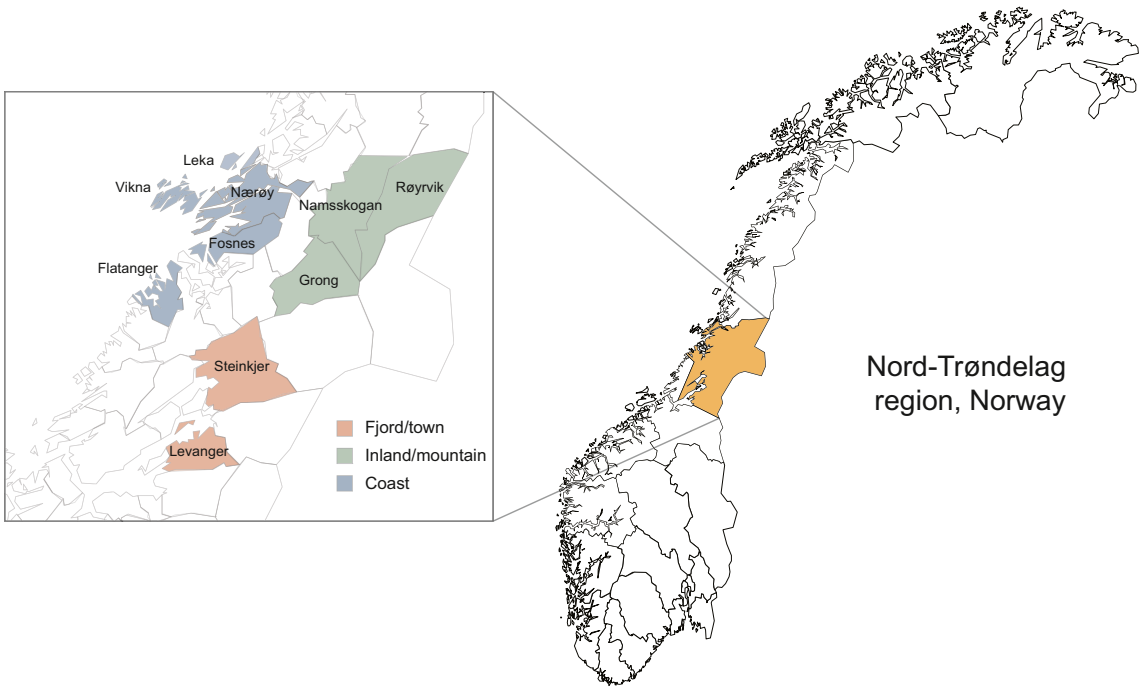

Fig. 1. Map of the Nord-Trøndelag region, Norway, and the selected geographical areas (coast, fjord/town, inland/mountain) in the study.

polypropylene tubes (Thermo Scientific) and stored at −80 °C at the HUNT Biobank. The selected samples were shipped on dry ice to our laboratory, where they were stored at −20 °C until analysis (~2 months).

2.3. Trace element analysis

The sample preparation was performed in a clean laboratory (ISO 6) to minimize contamination from the surroundings, paying strict attention to contamination control in all steps. Approximately 0.7 mL of blood was pipetted (Rainin E-Man Hybride, Mettler Toledo, Oakland, CA, USA) into 20 mL pre-cleaned teflon vessels (TFM PTFE UC). The pipette tips (Bioclean) were washed with ultrapure water (PURELAB Option-Q, ELGA, UK) before use. The precise mass of each blood sample was measured (Sartorius balance with Sartorius SartoCollect Software, Krugersdorp, South Africa) and converted back to volume by using the average density of whole blood (1.06 g/mL) (Trudnowski and Rico, 1974). Then 1.0 mL ultrapure concentrated nitric acid was added using a 5 mL bottle-top dispenser (Seastar Chemicals, Sidney, BC, Canada). The ultrapure nitric acid was produced at NTNU from p.a. grade nitric acid (Merck, Darmstadt, Germany) using a quartz sub-boiling distillation system (SubPur, Milestone, Shelton, CT, USA). The samples were digested using a high-performance microwave reactor (UltraClave, Milestone, Italy), where the temperature was gradually increased from 20 °C to 220 °C over 30 min, and then left for 20 min at 220 °C. The digested samples were decanted into pre-cleaned 15 mL polypropylene vials (VWR, European Catalogue no. 525-0461, batch no. 142CB, PA, USA) and diluted to approximately 15 mL with ultrapure water to achieve a final acid concentration of 0.6 M. The final weight of the diluted samples was measured with an analytical balance and converted to volume (density 0.6 M HNO_3: 1.0167 g/mL).

Trace element concentrations were measured using high-resolution inductively coupled plasma mass spectrometry (HR-ICP-MS, Thermo Finnigan Element 2, Thermo Finnigan, Bremen, Germany). The sample introduction system consisted of a fully automated sampling system with inline dilution integrated into the autosampler (SC2-DX-FAST ESI), a concentric PFA-ST nebulizer combined with a quartz microcyclonic Scott spray chamber with auxiliary gas port, aluminum sample and skimmer cones, and an O-ring-free quartz torch and 2.5 mm injector (Elemental Scientific, Omaha, NE, USA). The radio frequency power was set to 1350 W; nebulizer and T-connection sample gas flow were 0.75 and 0.55 L/min, respectively. Cooling gas flow was 15.5 L/min; auxiliary gas flow 1.1 mL/min and additional gas consisted of 10% methane in argon with flow rate of 0.01 L/min.

Two multi-element stock solutions (Elemental Scientific, Omaha, NE, USA) were used for the instrument calibration, one serving as a calibrating solution and the other as a quality control. Four different dilutions of the calibrating solution were prepared to cover the element concentration ranges. The solutions were matrix matched for 0.6 M nitric acid and main element concentrations (160 mg/L Na and 115 mg/L K). Na- and K-solutions were prepared from single element standard solutions (10,000 ppm, Spectrapure Standards AS, Oslo, Norway). An internal standard containing 1 μg/L of Re was automatically mixed with the sample in the prepFAST system. The elements were determined at three different resolutions, low (LR 400; Be, Cd, Cs, Au, In, Pb, Hg, Tl, Sn, and W), medium (MR 5000; B, Ca, Cr, Cu, Ga, Fe, Mg, Mn, Mo, Ni, Rb, Sc, Ag, Sr, and Zn), and high (HR 10000; As, Br, and Se).

2.4. Analytical quality control

To test for possible element leaching and contamination, blood collection tubes, pipet tips, polypropylene vials, flasks, and ultrapure acid used in the sample preparations were checked prior to the analysis. In total, concentrations of 58 elements (Ag, Al, As, Au, B, Ba, Be, Bi, Ca, Cd, Ce, Co, Cr, Cs, Cu, Dy, Er, Eu, Fe, Ga, Gd, Ge, Hg, Ho, In, Ir, La, Li, Lu, Mg, Mn, Mo, Nb, Nd, Ni, Pb, Pd, Pr, Pt, S, Sb, Sc, Se, Sm, Sn, Sr, Ta, Tb, Th, Tl, Tm, U, V, W, Y, Yb, Zn, and Zr) were measured using HR-ICP-MS. Elements found to be largely below the limits of detection (LOD) or potentially present as contaminants (assessed by evaluating results from leakage tests and blanks) were excluded from the analysis, leaving a total of 28 elements in the study. To check for instrumental drift, one of the multi-element standards was analyzed for every 20 samples. In each sample batch (n = 80 samples), one sample of the certified reference material Seronorm Level 1 (Sero, Norway, Supplementary Table S1) and two samples of one healthy volunteer blood specimen were analyzed to verify the accuracy of the instrument. In addition, four sample blanks (0.6 M HNO_3) were included in each batch. Blanks and control samples had an

alternating position in each batch. The stability of the instrument was controlled by checking the internal standard concentrations and argon signals, while the analytical recovery was calculated by dividing the measured value by the certified value.

2.5. Statistical analyses

To study associations between whole blood trace element concentrations and the geographical areas (coastal, fjord/town and inland/mountain) we applied linear regression models: We adjusted for sex and age (10-year categories) ("Model 1"), and further adjusted for socio-demographic factors previously reported to be associated with trace element blood concentrations: body mass index (BMI, categorized according to WHO recommendations as <25.0, 25.0–29.9, and ≥30 kg/m^2), education (<10, 10–12 and ≥13 years), and income (after-tax equivalent income – EU-equivalent scale, divided into quartiles) ("Model 2"). Lastly, we adjusted for intercorrelated trace elements (Spearman's rank correlation coefficient $|r_s| > 0.5$), specifically As-Hg ($r_s = 0.61$), Ca-Fe ($r_s = -0.59$), Cs-Rb ($r_s = 0.54$), Cr-Ni ($r_s = 0.77$), Fe-Zn ($r_s = 0.56$), and Hg-Se ($r_s = 0.54$) ("Model 3"). Prior to statistical analyses, trace elements which showed deviations from normal distribution (evaluated using histograms) were natural log transformed. Trace element concentrations < LOD (set equal to 3 times the standard deviation of blank samples) were replaced with a value equal to LOD/2. We excluded Be, Sc and W from the statistical models due to concentrations < LOD in over 33% of the samples. The levels of significance were corrected using the Bonferroni multiple comparisons procedure. Because the total number of tests were 50, a p-value of 0.001 corresponds to a Bonferroni significance value (q) 0.05.

We applied general linear models to estimate marginal effects (to obtain interpretable trace element concentrations), and compared trace element blood concentrations for different socio-demographic and lifestyle categories: crude estimates ("Unadjusted model"), adjusted for sex and age ("Sex and age adjusted model"), and further adjusted for geographical area, waist circumference (categorized according to WHO recommendations (2011), men: <94 cm (normal), 94–102 cm (abdominal overweight), and >102 cm (abdominal obese), women: <80 cm (normal), 80–88 cm (abdominal overweight), and >88 cm (abdominal obese)), BMI, education, income, self-reported smoking status (never smokers, former smokers and current smokers), self-reported fatty fish consumption (specifically, salmon, trout, herring, mackerel, and redfish: <4 meals monthly, 1–3 meals weekly and ≥4 meals weekly), and alcohol intake (divided into quartiles of daily amount of grams of alcohol consumed: 0 (abstainers), 0.2–2.6, 2.7–6.0 and >6.0 g/day (Rasouli et al., 2013)), based on self-reported consumption of alcohol units (beer, wine and spirits) and intercorrelated trace elements ("Fully adjusted model"). Sampling weights based on sex, age, and geographic area, were included to provide accurate estimates reflecting the population in the three areas.

All statistical analyses were repeated after excluding outliers, in this study defined as measurements with values <1st quartile − 1.5 × interquartile range (IQR) or >3rd quartile + 1.5 × IQR (essential trace elements), and >3rd quartile + 1.5 × IQR (non-essential trace elements). Outliers did not seem to influence the obtained results, and presented results therefore include all individuals with available trace element and covariate data. To account for the potential of false discovery due to multiple testing, *p*-values were corrected using the Bonferroni procedure and p-values adjusted for multiple testing (*q*-values) less than 0.05 was considered statistically significant. Statistical analyses were performed using Stata 16 (StataCorp, TX, USA), SPSS 24 (SPSS, Inc., IL, USA) and R v3.5.1 (The R Foundation for Statistical Computing, Austria).

2.6. Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK 2010/2947), and all participants gave a written informed consent.

3. Results

Characteristics of the participants are shown in Table 2, while the distributions of the 28 trace elements are summarized in Table 3. Trace element concentrations in the current study were generally in agreement with concentrations reported in 16 recent studies (Table 1).

3.1. Differences in trace element blood concentrations between the geographical areas

Whole blood trace element concentrations in the three geographical areas (coastal, fjord/town and inland/mountain) were compared. Table 4 presents the regression coefficient β (μg/L or mg/L) for the normally distributed elements, and the percentage of difference (%) for the non-normally distributed elements. In models adjusted for age and sex, we found statistically significant (after correction for multiple testing) differences in 19 trace element concentrations: 12 (As, B, Br, Ga, Au, Fe, Mg, Hg, Mo, Se, Tl, and Zn) and 17 (As, B, Br, Ca, Cs, Ga, Au, Pb, Mn, Hg, Mo, Rb, Se, Ag, Tl, Sn, and Zn) trace element concentrations were different when we compared the fjord/town and the inland/mountain populations to the coastal population, respectively. Adjusted for sex

Table 2
General characteristics of the study population.

Characteristic	Total (n = 1011)	Men (n = 506)	Women (n = 505)
Mean age, years (SD)	50.0 (17.6)	50.2 (17.6)	49.9 (17.7)
Age group (years), n (%)			
20–29	167 (16.5)	82 (16.2)	85 (16.8)
30–39	169 (16.7)	86 (17.0)	83 (16.5)
40–49	170 (16.8)	85 (16.8)	85 (16.8)
50–59	168 (16.6)	85 (16.8)	83 (16.5)
60–69	169 (16.7)	84 (16.6)	85 (16.8)
≥70	168 (16.6)	84 (16.6)	84 (16.6)
Geographical area, n (%)			
Inland/mountain	335 (33.2)	166 (32.8)	169 (33.5)
Fjord/town	336 (33.2)	169 (33.4)	167 (33.0)
Coastal	340 (33.6)	171 (33.8)	169 (33.5)
Waist circumference (cm), n (%)			
Men: <94, Women: <80	296 (29.3)	199 (39.3)	97 (19.2)
Men: 94–102, Women: 80–88	291 (28.8)	162 (32.0)	129 (25.5)
Men: >102, Women: >88	424 (41.9)	145 (28.7)	279 (55.3)
Mean body mass index kg/m^2 (SD)[a]	27.3 (4.5)	24.6 (4.1)	27.0 (4.9)
Body mass index group (kg/m^2), n (%)			
<25.0	316 (31.4)	125 (24.8)	191 (38.0)
25.0–29.9	438 (43.5)	255 (50.6)	183 (36.5)
≥30	252 (25.1)	124 (25.5)	128 (25.5)
Education (years), n (%)			
<10	249 (24.7)	133 (26.4)	116 (23.0)
10–12	524 (52.0)	276 (54.8)	248 (49.2)
≥13	235 (23.3)	95 (18.8)	140 (27.8)
Economic status level, n (%)[b]			
Quartile 1 (lowest)	252 (24.9)	116 (22.9)	136 (26.9)
Quartile 2	239 (23.6)	115 (22.7)	124 (24.6)
Quartile 3	288 (28.5)	154 (30.5)	134 (26.5)
Quartile 4	232 (23.0)	121 (23.9)	111 (22.0)
Mean alcohol intake, g/day (SD)	4.4 (5.4)	5.8 (6.2)	2.9 (4.0)
Alcohol intake in g/day in group, n (%)			
Abstainers	280 (27.7)	101 (20.0)	179 (35.4)
<2.7	232 (23.0)	94 (18.6)	138 (27.3)
2.7–6.0	248 (24.5)	135 (26.7)	113 (22.4)
≥6.0	251 (24.8)	176 (34.7)	75 (14.9)
Smoking status, n (%)			
Never smokers	433 (42.8)	208 (41.1)	225 (44.5)
Former smokers	373 (36.9)	200 (39.5)	173 (34.3)
Current smokers	205 (20.3)	98 (19.4)	107 (21.2)
Fatty fish consumption, n (%)[c]			
<4 meals monthly	399 (39.5)	206 (40.7)	193 (38.2)
1–3 meals weekly	513 (50.7)	252 (49.8)	261 (51.7)
≥4 meals weekly	99 (9.8)	48 (9.5)	51 (10.1)

[a] Data available for 504 (99.6%) men and 502 (99.4%) women.
[b] Data available for 504 (99.6%) men and 504 (99.8%) women.
[c] Fatty fish includes salmon, trout, herring, mackerel, and redfish.

Table 3
Whole blood trace element concentrations of 1011 participants (20–91 years) in the HUNT3 Survey. LOD: Limit of detection.

Element	LOD	<LOD (%)	Mean	Range	Geometric mean	Median	Percentiles			
							5%	25%	75%	95%
As (μg/L)	0.46	4.0	4.29	<0.46–70.5	2.64	2.55	0.61	1.36	4.95	14.5
Be (μg/L)	0.0096	81.8	<0.0096	<0.0096–0.0260	<0.0096	<0.0096	<0.0096	<0.0096	<0.0096	0.0122
B(μg/L)	2.2	0	30.0	6.6–144	27.2	27.7	13.1	20.6	36.9	55.2
Br (mg/L)	0.11	0	1.60	0.26–7.10	1.51	1.53	0.86	1.27	1.84	2.37
Cd (μg/L)	0.016	0.1	0.54	<0.016–4.65	0.36	0.31	0.11	0.20	0.56	1.87
Ca (mg/L)	0.14	0	59.1	47.8–71.3	59.0	59.0	52.3	56.6	61.6	65.6
Cs (μg/L)	0.0039	0	4.68	1.45–36.0	4.44	4.38	2.66	3.62	5.39	7.43
Cr (μg/L)	0.40	31.5	0.93	<0.40–46.2	0.58	0.59	<0.40	<0.40	1.08	2.26
Cu (mg/L)	0.0013	0	1.03	0.44–2.18	1.01	1.01	0.82	0.92	1.10	1.27
Ga (μg/L)	0.010	0	0.078	0.020–1.81	0.073	0.073	0.046	0.061	0.085	0.112
Au (μg/L)	0.0057	21.6	0.0147	<0.0057–0.287	0.0097	0.0093	<0.0057	0.0068	0.0142	0.0392
In (μg/L)	0.002	0.1	0.032	<0.002–0.079	0.029	0.029	0.016	0.024	0.037	0.060
Fe (mg/L)	0.133	0	543	378–693	541	541	468	508	575	631
Pb (μg/L)	0.41	0	21.5	3.46–219	18.8	18.6	8.9	13.6	25.4	45.5
Mg (mg/L)	0.015	0	39.7	27.9–61.3	39.6	39.6	33.9	37.3	42.0	45.9
Mn (μg/L)	0.40	0	9.52	3.75–66.4	9.11	8.92	5.81	7.51	10.8	14.9
Hg (μg/L)	0.036	0	3.63	0.24–21.6	2.74	2.73	0.84	1.58	4.66	9.69
Mo (μg/L)	0.43	3.9	0.95	<0.43–8.14	0.83	0.81	0.44	0.62	1.07	1.78
Ni (μg/L)	0.22	11.9	0.71	<0.22–9.71	0.50	0.49	<0.22	0.31	0.85	1.72
Rb (μg/L)	0.16	0	2250	1266–3789	2220	2228	1715	1977	2478	2877
Sc (μg/L)	0.0089	51.1	<0.0089	<0.0089–0.615	<0.0089	<0.0089	<0.0089	<0.0089	0.0112	0.0155
Se (μg/L)	6.5	0	102.0	51.4–255.7	100.2	99.3	75.4	89.5	112.8	136.9
Ag (μg/L)	0.039	16.7	0.160	<0.039–1.019	0.112	0.122	<0.039	0.070	0.202	0.424
Sr (μg/L)	0.13	0	18.6	8.6–62.5	18.0	17.4	12.2	14.9	21.2	29.4
Tl (μg/L)	0.0011	0	0.028	0.009–0.191	0.026	0.026	0.016	0.022	0.031	0.047
Sn (μg/L)	0.10	19.8	0.55	<0.10–5.62	0.24	0.20	<0.10	0.12	0.37	3.13
W (μg/L)	0.022	60.2	<0.022	<0.022–0.541	<0.022	<0.022	<0.022	<0.022	0.027	0.055
Zn (mg/L)	0.004	0	7.5	3.8–11.4	7.5	7.5	5.9	6.8	8.2	9.1

Table 4
Associations between whole blood trace element concentrations and geographical area given as the regression coefficient β (μg/L or mg/L) for the normally distributed elements, and the percentage of difference (%)[a] for the non-normally distributed elements (ln-transformed) with 95% confidence intervals (CI), using the coastal area as the reference.

Element	Model 1 (n = 1011)[b]		Model 2 (n = 1003)[c]		Model 3 (n = 1003)[d]	
	Fjord/town	Inland/mountain	Fjord/town	Inland/mountain	Fjord/town	Inland/mountain
As (%)	−47.2 (−54.5; −38.7)***	−55.5 (−61.7; −48.4)***	−48.6 (−55.9; −40.1)***	−55.5 (−61.8; −48.3)***	−33.1 (−42.0; −22.8)***	−41.0 (−49.0; −31.7)***
B (%)	11.2 (4.0; 18.8)*	−13.5 (−19.3; −7.3)***	8.7 (1.6; 16.4)*	−13.4 (−19.2; −7.2)***	–	–
Br (%)	−11.8 (−16.2; −7.2)***	−11.7 (−15.4; −7.7)***	−13.2 (−17.6; −8.6)***	−11.6 (−15.4; −7.6)***	–	–
Cd (%)	−13.2 (−17.6; −8.6)	−11.6 (−15.4; −7.6)	4.3 (−15.8; 9.2)	6.6 (−6.7; 21.7)	–	–
Ca (mg/L)	−0.13 (−0.67; 0.41)	−1.58 (−2.10; −1.06)***	−0.23 (−0.78; 0.33)	−1.51 (−2.03; −0.99)***	0.19 (−0.33; 0.71)	−1.33 (−1.83; −0.83)***
Cs (%)	0.3 (−4.3; 5.2)	11.8 (6.2; 17.6)***	−0.7 (−5.5; 4.3)	11.7 (6.0; 17.7)***	−2.2 (−6.5; 2.3)	2.6 (−2.1; 7.6)
Cr (%)	12.6 (−2.4; 30.1)	10.8 (−4.1; 27.9)	15.5 (−0.4; 34.0)	10.5 (−4.5; 27.9)	5.3 (−4.0; 15.6)	−1.3 (−10.3; 8.5)
Cu (μg/L)	18.6 (−2.9; 40.1)	16.0 (−5.1; 37.0)	26.2 (4.0; 48.4)*	16.9 (−3.7; 37.6)	–	–
Ga (%)	10.5 (5.2; 16.0)***	21.8 (16.5; 27.3)***	11.3 (6.0; 16.8)***	21.6 (16.2; 27.2)***	–	–
Au (%)	18.0 (4.6; 33.1)*	−13.9 (−23.6; −3.0)*	16.2 (2.7; 31.4)*	−14.7 (−24.4; −3.7)*	–	–
In (%)	4.3 (−3.0; 12.2)	6.1 (−11.4; 0.2)	4.5 (−3.2; 12.8)	5.9 (−11.2; 0.5)	–	–
Fe (mg/L)	11.8 (5.1; 18.4) **	6.6 (−0.6; 13.8)	13.7 (7.0; 20.4)***	5.9 (−1.3; 13.2)	7.1 (1.6; 12.5)*	−3.5 (−9.9; 2.9)
Pb (%)	−1.1 (−8.4; 6.9)	15.6 (6.9; 25.0)**	0.0 (−7.4; 8.0)	15.7 (7.0; 25.1)**	–	–
Mg (mg/L)	0.62 (0.04; 1.21)*	0.13 (−0.44; 0.70)	0.76 (0.16; 1.37)*	0.14 (0.43; 0.72)	–	–
Mn (%)	4.6 (0.0; 9.5)	5.7 (1.0; 10.6)*	4.1 (−0.8; 9.2)	5.5 (0.7; 10.4)*	–	–
Hg (%)	−29.5 (−36.0; −22.2)***	−32.5 (−38.5; −26.0)***	−31.4 (−38.1; −24.1)***	−33.3 (−39.2; −36.8)***	−13.1 (−20.2; −5.4)*	−14.7 (−21.3; −7.5)***
Mo (%)	11.9 (2.8; 21.9)*	16.4 (7.8; 25.7)**	12.8 (3.4; 22.9)*	18.1 (9.4; 27.6)***	–	–
Ni (%)	11.9 (−2.2; 28.1)	15.0 (0.0; 32.3)	12.0 (−3.1; 29.4)	14.9 (−0.3; 32.4)	1.4 (−7.5; 11.2)	7.3 (−2.2; 17.7)
Rb (μg/L)	36 (−22; 94)	227 (167; 288)***	41 (−17; 100)	235 (174; 296)***	45 (−8; 98)	178 (123; 232)***
Se (%)	−4.6 (−7.3; −1.8)*	−4.0 (−6.6; −1.0)*	−5.8 (−8.2; −2.8)***	−3.9 (−6.8; −1.0)*	0.1 (−2.5; 2.6)	2.2 (−0.5; 4.9)
Ag (%)	4.3 (−8.8; 19.3)	−32.6 (−41.4; −22.6)***	3.4 (−9.8; 18.5)	−33.1 (−41.8; −23.0)***	–	–
Sr (%)	1.2 (−2.8; 5.4)	−0.7 (−4.6; 3.4)	2.3 (−2.0; 6.7)	0.5 (−4.5; 3.7)	–	–
Tl (%)	8.1 (3.0; 13.4)*	28.1 (21.0; 35.6)***	7.2 (2.1; 12.6)*	27.5 (20.4; 35.0)***	–	–
Sn (%)	14.6 (−4.0; 36.7)	−26.2 (−36.5; −14.1)***	12.9 (−5.8; 35.5)	−25.9 (−36.5; −13.6)**	–	–
Zn (mg/L)	0.28 (0.15; 0.42)***	0.21 (0.07; 0.36)*	0.31 (0.17; 0.45)***	0.20 (0.05; 0.35)*	0.18 (0.05; 0.30)*	0.15 (0.01; 0.29)*

[a] Percentage of difference calculated as 1 subtracted from the anti-ln of the β regression coefficient for ln-transformed trace element blood concentrations.
[b] Adjusted for sex and age.
[c] Adjusted for sex, age, body mass index, education. and income.
[d] Adjusted for sex, age, body mass index, education, income and for moderately/highly intercorrelated trace element concentrations (Spearman's correlation coefficient $|r_S| > 0.5$).
* $P < 0.05$.
** $P < 0.001$.
*** $P < 0.0001$.

and age, both the fjord/town and inland/mountain populations had lower concentrations of As (−47% and −56%), Br (−12% and −12%), Hg (−30% and −33%), and Se (−5% and −4%), and higher concentrations of Ga (+11% and +22%), Mo (+12% and +16%), Tl (+8% and +28%) and Zn (+0.3 mg/L and +0.2 mg/L), compared to the coastal population. Boxplots of unadjusted blood concentrations of As, Hg, Br and Se are presented in Fig. 2.

Differences in trace element concentrations between the geographical areas did not change substantially when further adjusted for BMI, education, and income (Table 4): Lower As (−49% and −56%), Br (−13% and −12%), Hg (−31% and −33%), and Se (−6% and −4%), and higher Ga concentrations (+11% and +22%), Mo (+13% and +18%), Tl (+7% and +28%) and Zn (+0.3 mg/L and +0.2 mg/L) when comparing the fjord/town and the inland/mountain populations to the coastal population. Additionally, slightly higher concentrations of Cu (+26 μg/L) were observed in the fjord/town population, compared to individuals on the coast in models adjusted for sex, age, BMI, education, and income.

In models further adjusted for intercorrelated trace elements (Table 4), the observed associations remained similar, but were attenuated, except for Se where there was little evidence for differences in Se concentrations between the geographical areas: Lower As (−33% and −41%) and Hg (−13% and −15%), and higher Zn (0.2 mg/L and 0.2 mg/L) in the fjord/town and inland/mountain populations compared to the coast.

3.2. Relationships between trace element concentrations and lifestyle and socio-demographic factors

We estimated marginal effects from the general linear models to obtain interpretable trace element concentrations for selected socio-demographic and lifestyle categories. The estimated marginal means with 95% confidence intervals for selected lifestyle and socio-demographic characteristics (age, sex, smoking, alcohol intake, BMI, waist circumference, and fatty fish intake) are summarized in Supplementary Tables S2–S26.

3.2.1. Age and sex

We found differences between men and women for 12 trace elements. In unadjusted models, higher concentrations of Br, Cd, Ca, Cu, and Mn were found in women, while higher concentrations of Ga, Fe, Pb, Mg, Rb, and Zn were found in men. These differences were statistically significant in adjusted models, except for Br, Ga, and Zn. In addition, higher concentrations of B were found in women in the fully adjusted model.

Differences in trace element concentrations between age categories were found for 14 trace elements (As, B, Ca, Cd, Cs, Fe, Au, Pb, Hg, Ag, Rb, Se, Sr, Zn) in unadjusted models. A trend for increasing concentrations with increasing age was found for As, B, Cd, Cs, Au, Pb, Hg, and Ag. In fully adjusted models, increasing concentrations with increasing age remained statistically significant, except for As and Cd.

3.2.2. Smoking

We found Cd and Rb concentrations to be associated with smoking. In current smokers, the concentration of Cd was more than fourfold higher compared to the never smokers in the adjusted model, while in former smokers the Cd concentrations were 50% higher compared to never smokers. Whole blood Cd concentrations in never smokers, former smokers and current smokers are shown in Fig. 3A. For Rb, higher concentrations were found in current smokers compared to never smokers, while no differences were found between former smokers and never smokers. Lower B concentrations were found in current smokers than in never smokers. However, this association was only significant in the age- and sex-adjusted model.

3.2.3. Alcohol intake

Increasing B, Cs and Pb concentrations were found with increasing alcohol intake, statistically significant in fully adjusted models. In unadjusted models, we found higher Se and Fe concentrations with increasing alcohol intake, while Cu concentrations were lower in individuals with an alcohol consumption in the third quartile compared to abstainers. Similar trends were observed in the fully adjusted models, but these were not statistically significant.

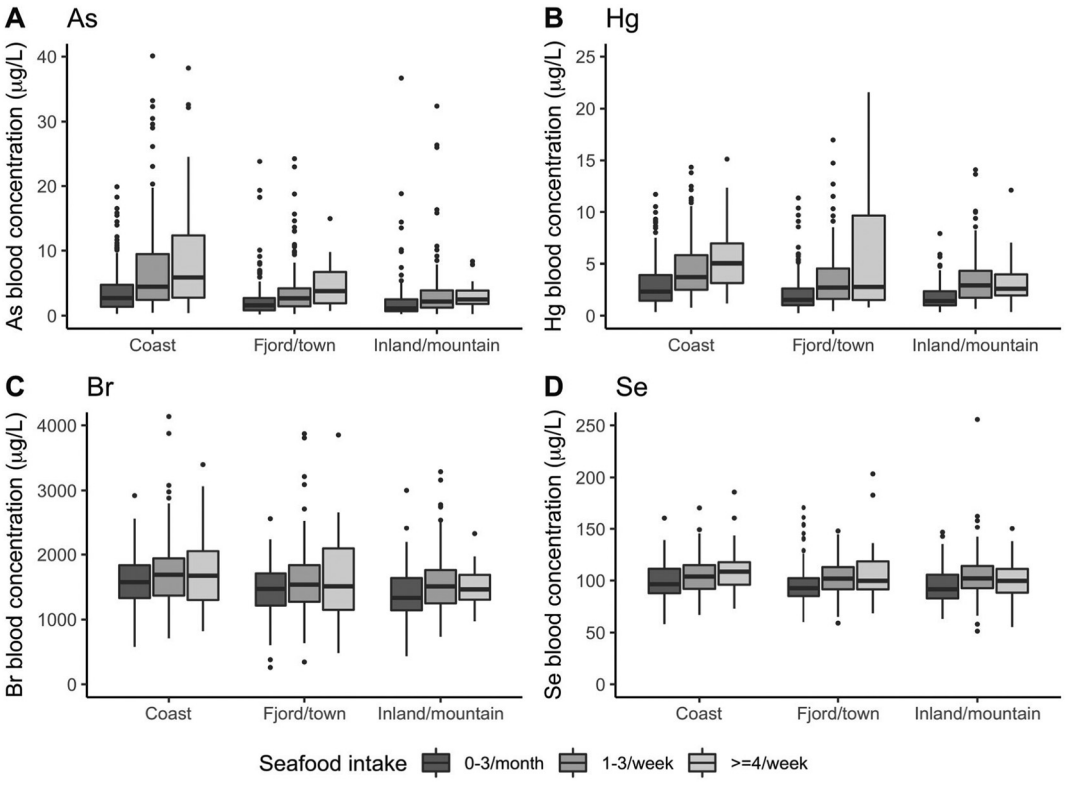

Fig. 2. Whole blood concentrations of A) As, B) Hg, C) Br, and D) Se in the three geographical areas (coast, fjord/town, inland/mountain), by fatty fish intake.

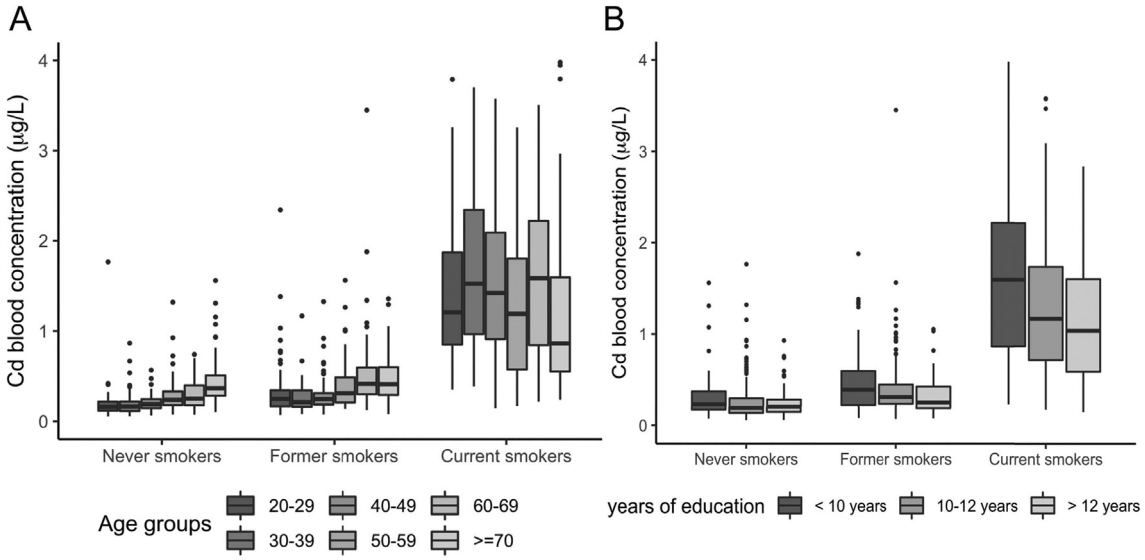

Fig. 3. Whole blood cadmium blood concentrations in never smokers, former smokers, and current smokers by A) 10-years age categories and B) years of education.

3.2.4. Fatty fish intake

In unadjusted models, increased blood concentrations of As, Hg, and Se were found with increasing intake of fatty fish, Fig. 2. However, in the fully adjusted model (including adjustment for intercorrelated trace elements), these differences were not statistically significant.

3.2.5. BMI and waist circumference

For BMI, we found negative associations for Br, Ca, and Zn concentrations, and a positive association for Mg. In addition, a positive association was found between BMI and waist circumference for Fe concentrations. However, none of these observations were statistically significant in the fully adjusted models.

3.2.6. Education and income

Decreasing Cd concentrations (Fig. 3B) were found with increasing levels of education and income in the unadjusted models. Further, increased concentrations of Cs and Se were found in the highest quartile of income, compared to the lowest quartile. In individuals with education ≥13 years or in the highest quartile of income, we found higher B concentrations compared to the lowest education level and quartile of income, respectively. However, these differences were not statistically significant in the fully adjusted model.

4. Discussion

In this large population-based study, we report whole blood trace element concentrations for 28 trace elements in the Nord-Trøndelag region, Norway. As the most comprehensive health study in Norway, the HUNT Study is an excellent source for human biomonitoring studies. By applying a sex-, age-, and area-stratified probability sampling design, we obtained a sample highly representative of the general population. Further, the access to a wide range of variables allowed us to compare trace element concentrations for a wide range of socio-demographic and lifestyle factors. In this work we highlight that geographical area, lifestyle, and selected socio-demographic characteristics are important factors associated with trace element concentrations.

4.1. Trace element concentrations in Trøndelag, Norway compared to other recent studies

Trace element concentrations in the region were generally comparable to levels reported in other recently published studies (Table 1) (Alimonti et al., 2011; Averina et al., 2020; Baeyens et al., 2014; Bárány et al., 2002; Birgisdottir et al., 2013; Caspersen et al., 2019; Fløtre et al., 2017; Goullé et al., 2005; Heitland and Köster, 2006; Meltzer et al., 2016; Nisse et al., 2017; Saravanabhavan et al., 2017; Snoj Tratnik et al., 2019; Wennberg et al., 2017; Yedomon et al., 2017; Zhang et al., 2015). Essential trace elements are generally metabolically well controlled, but concentrations may differ between countries due to diet, geographical variations, or characteristics of the cohorts. This may explain the generally minor differences we observed for B, Cr, Cu, Fe, Mg, Mn, Se, and Zn compared to other studies. For Zn, we detected slightly higher levels compared to some other studies, but comparable to our previous work (Syversen et al., 2021), This is likely to be related to differences in diet between countries, as Zn blood content depends to a large extent on the diet (Simon-Hettich et al., 2001). Similarly, Cu levels in HUNT were slightly higher than levels reported in Sweden (Wennberg et al., 2017) and Slovenia (Snoj Tratnik et al., 2019), while slightly lower than in a large study of pregnant women in Norway (Caspersen et al., 2019). However, results were similar to those reported in our previous work (Syversen et al., 2021). Our Mn results agree with our previous study (Syversen et al., 2021), and are in accordance with expected Mn levels in a non-occupationally exposed population.

In human biomonitoring studies, focus is often on toxic trace elements, particularly Cd, Hg, and Pb, due to their negative health effects. Compared to recent publications, concentrations of Cd and Pb in this work are in broad agreement with expected levels in individuals with no or little occupational exposure and suggest low exposure to toxic elements in this region. This is in accordance with our expectations, as the Nord-Trøndelag region is largely rural, and the industrial pollution is considered low (Langhammer et al., 2000). On the other hand, Hg concentrations were slightly higher in our study than in some other studies (Alimonti et al., 2011; Bárány et al., 2002; Heitland and Köster, 2006; Nisse et al., 2017; Saravanabhavan et al., 2017; Snoj Tratnik et al., 2019), but comparable to two previous Norwegian studies (Birgisdottir et al., 2013; Syversen et al., 2021). Chronic low exposure to Hg has been linked to an increased risk of neurodevelopmental effects in infants and children (Ha et al., 2017). Although suggested to be associated with cardiovascular diseases in adults (Mozaffarian, 2009), later studies have shown conflicting results (Downer et al., 2017; Mozaffarian et al., 2011). In the current study, in individuals consuming 0–3 meals of fatty fish monthly, Hg concentrations were comparable to those reported in a German population with similar fish intake (GM 1.98 μg/L and 2.0 μg/L, respectively) (Wilhelm et al., 2004). Further, our Hg results are comparable to those reported in studies among high

seafood consumers in e.g., Sweden (Johnsson et al., 2004) and Finland (Airaksinen et al., 2011). The relatively high Hg concentrations reported in the HUNT3 participants may therefore reflect the importance of fish in the Norwegian diet (Birgisdottir et al., 2013; Jenssen et al., 2012). Hg in fish varies considerably depending on the type of fish and where it was caught (Jenssen et al., 2012). The fish consumed by HUNT participants most likely comprise both pelagic and freshwater fish. However, the HUNT study does not contain detailed data on fish species consumed or origin of fish, which limited the potential of exploring these associations further.

4.2. Differences in trace element blood concentrations between geographical areas

We found geographical residency to be a key factor associated with trace element concentrations. In total, differences were found for 19 trace elements (As, B, Br, Ca, Cs, Ga, Au, Fe, Pb, Mg, Mn, Hg, Mo, Rb, Se, Ag, Tl, Sn and Zn) comparing concentrations in the coastal population to either the fjord/town or the inland/mountain populations. For non-occupationally exposed individuals, the major sources of trace elements are through food, water and air. Although the Nord-Trøndelag region is mostly rural, there may be regional differences in exposure through inhalation and from drinking water (Husby, 2014), but these differences are likely to be minor compared to differences in the diet, which will be a combination of local, national, and international food products. The drinking water quality in the Nord-Trøndelag region is considered good, and mainly to be within the Norwegian and international guidelines (Husby, 2014).

Concentrations of As, Br, Hg and Se were lower both in fjord/town and inland/mountain populations compared to the coastal population, which might indicate an association between the marine environment and concentrations of these trace elements. Our findings are in line with a previous study from Norway, which found higher blood concentrations of As, Hg and Se among individuals living on the coast compared to those living in the inland (Birgisdottir et al., 2013). A major source for these elements in terrestrial ecosystems is transport through the atmosphere from ocean to land (Steinnes, 2009; Steinnes and Lierhagen, 2017). Arsenic is present in seawater and is released into the atmosphere as sea salt aerosols. Previous studies of moss and soil across Norway have showed large geographical variations for many elements, including higher levels of Br and Se in coastal areas (Steinnes et al., 2011; Steinnes and Lierhagen, 2017). These results agree with our findings of higher levels of Br and Se in the coastal population compared to the fjord/town and inland/mountain areas. Higher Br concentrations have been found in drinking water close to the coast than in inland/mountain areas (Husby, 2014), in line with our Br blood results. Although not likely to affect the observed differences between the geographical areas, we note that the analytical recovery of Br in this study was only 35%, due to loss of Br during the acid digestion process (Mesko et al., 2016).

Fish and seafood are well known dietary sources of As, Br, Hg and Se (Mergler et al., 2007). Hg levels vary greatly between types and species of seafood with the highest concentration in large predatory fish species (Jenssen et al., 2012; Mergler et al., 2007). In our study, we did not find any substantial differences in fatty fish consumption between the three geographical areas. However, there was a tendency towards a lower proportion of the population consuming <4 meals of fatty fish monthly in the fjord/town area compared to the coast and the inland/mountain area, and a slightly higher proportion of individuals consuming ≥4 meals of fatty fish weekly on the coast compared to the fjord/town and the inland/mountain region. However, the number of individuals in the 'high consuming' group was limited (only ~20–50 individuals in each area), making detailed sub-analyses difficult to perform in our study. To summarize, although intake of fatty fish is important for particularly As and Hg blood concentrations, our results suggest that the observed differences in As, Br, Hg and Se blood concentrations may not be explained by intake of fatty fish alone. Previous studies from New Zealand ('t Mannetje et al., 2021), and Norway (Jenssen et al., 2012), have suggested that place of residence is a determinant of blood Hg independent of fish consumption (Jenssen et al., 2012), in line with our findings. Additionally, self-capture of fish and the locations where the fish was caught are potentially significant factors determining Hg blood levels (Jenssen et al., 2012; Måge and Frantzen, 2009). The HUNT Study does not contain detailed information regarding fatty fish consumption (e.g., portion size, type of fish and where it was caught) which could be important factors explaining the observed regional differences in the current study. Future studies should attempt to investigate these associations further.

We found As, Se and Hg to be intercorrelated, and therefore we included these elements in the fully adjusted models. When adjusted for Hg, little evidence for regional differences in Se concentrations was found. This may possibly be explained by Se being an antagonist of Hg, affecting absorption, distribution and elimination of Hg (Jadán-Piedra et al., 2017). To address this aspect in more detail, we would need data for speciation of inorganic and organic Hg. On the other hand, differences in As and Hg concentrations between the geographical areas were only slightly attenuated adjusting for Hg and As and Se concentrations, respectively.

We found 15% higher Pb concentrations in the inland/mountain compared to the coastal population, also in the fully adjusted models. Humans are exposed to Pb through food, drinking water, air and dust. According to the European Food Safety Authority (EFSA), grain products, milk and dairy products, non-alcoholic beverages, and vegetables are the major dietary lead sources in the general population (EFSA, 2010). However, studies in e.g. Norway and Sweden have reported associations between Pb blood concentrations and lead-shot cervid meat (Meltzer et al., 2013; Wennberg et al., 2017). Previous studies in Norway have reported higher consumption of game meat in inland than in coastal areas (Knutsen et al., 2013; Knutsen et al., 2019). Since there is no information of consumption of game meat in the HUNT Study we were not able to further explore this association in our study.

Ga and Tl are widely used in electronics and semiconductors and may be considered as emerging pollutants (White and Shine, 2016; Zhao et al., 2020). It is important to establish levels of these trace elements in general populations before our environment becomes significantly contaminated by these elements. We found higher concentrations of Ga and Tl in the fjord/town and inland/mountain populations, compared to the costal population. To our knowledge, few studies have reported how Ga and Tl blood levels vary in the general population. Compared to previous studies, we found Ga and Tl blood concentrations comparable to those reported in healthy volunteers in France (Goullé et al., 2005), and lower compared to optoelectronic industry workers in Taiwan (Liao et al., 2004).

4.3. Relationships between trace element concentrations and lifestyle and socio-demographic characteristics

We found trace element concentrations to vary with lifestyle and socio-demographic characteristics, including sex, age, education, economic status, BMI, waist circumference, alcohol intake, smoking status and fatty fish intake. Differences in trace element concentrations were particularly evident between men and women, and across age categories.

We found the concentrations of B, Br, Cd, Ca, Cu, and Mn to be higher in women, and Ga, Fe, Pb, Mg, Rb, and Zn to be higher in men. We observed similar differences in fully adjusted models for all trace elements, except for Br and Zn. Our results are generally in agreement with previous studies reporting differences between men and women (Bárány et al., 2002; Clark et al., 2007; Jain and Choi, 2015; Kim et al., 2014; Vahter et al., 2007), and suggest sex to be important for trace element status. Differences in concentrations of some trace elements between men and women may be due to the lower concentration of erythrocytes

in women, so elements like Fe and Pb, which are present primarily in erythrocytes, will generally be lower in whole blood in women than in men (Iyengar, 1987). Higher Cd and Mn concentrations in women are in line with earlier reported findings (Alimonti et al., 2011; Bárány et al., 2005; Clark et al., 2007), and could potentially be explained by competitive gastrointestinal absorption for Cd, Mn, and Fe, and the lower Fe stores in women (Vahter et al., 2007).

The elements As, B, Cd, Cs, Au, Pb, Hg, and Ag were found to increase with increasing age, and we also found differences in some age groups for Fe, Rb, Se, Sr and Zn. These associations were significant also in fully adjusted models (except for As, after adjustment for Hg), suggesting age to be associated with concentrations of many trace elements. Increased concentrations with increasing age were particularly evident for trace elements with a slow elimination from the body, notably Cd and Pb (Gil and Hernández, 2015).

We found Cd and Rb concentrations to be higher in current smokers compared to never smokers. Compared to never smokers, former smokers had ~50% higher Cd concentrations, while current smokers had more than fourfold higher Cd concentrations than never smokers. Smoking is a well known source of some trace elements, particularly Cd (Chiba and Masironi, 1992), and earlier studies have also reported manifold higher Cd blood concentrations in smokers (Whitfield et al., 2010). We are not aware of studies investigating how Rb concentrations vary with smoking status. Rb is a non-toxic trace element with no biological function. However, Rb generally behaves biologically very much like K, and K levels have been observed to be increased in smokers (Falk et al., 2021).

Alcohol intake was associated with higher B, Cs, Fe, Pb, and Se, and lower Cu blood concentrations. These associations were also present in fully adjusted models for B, Cs, and Pb. A few studies have investigated the association between alcohol consumption and concentrations of trace elements, and have suggested decreased Cu (Shibazaki et al., 2017), and increased Pb (Grandjean et al., 1981; Kristiansen et al., 1997; Whitfield et al., 2010) and Se (Galan et al., 2005; Whitfield et al., 2010) concentrations with increased alcohol consumption, in line with our findings.

Increased blood concentrations of As, Hg and Se were found with increasing intake of fatty fish (salmon, trout, herring, mackerel, and redfish). However, when further adjusted (including intercorrelated trace elements), these differences were not statistically significant. It should be noted that some fish and seafood contain high levels of organic As which may give transiently increased levels of As in blood, and this is not a health hazard. As previously discussed, our results might indicate that geographical residency, specifically proximity to the coast, is associated with increased concentrations of these trace elements, although factors including the species of fish consumed, portion size, and where the fish was caught should be considered in future studies.

We found BMI to be negatively associated with Br, Ca, and Zn, and positively associated with Mg. In addition, a positive association was found between Fe and BMI and waist circumference. However, in fully adjusted models, no differences in trace element concentrations were observed, suggesting that differences may be linked to other factors than body composition. Previous studies have suggested an association between body composition and concentrations of some trace elements, including Cu, Pb, and Zn (Gu et al., 2020; Rios-Lugo et al., 2020; Wang et al., 2015).

Increasing Cd and decreasing B, Cs, and Se blood concentrations were found to be associated with decreasing levels of education and income, in line with previous studies (see below). However, in the fully adjusted models (including smoking) these associations were attenuated, and not statistically significant after adjustment for multiple testing. B is a trace element that is naturally present in fruit and vegetables. In HUNT4, participants with higher education levels had a higher intake of fruit and vegetables than individuals with less education (HUNT Research Center, 2019), potentially explaining our findings. Previous studies have found lower Cd concentrations to be associated with higher income (Ahn et al., 2017), and with higher education levels (Caspersen et al., 2019; Whitfield et al., 2010), while lower concentrations of Se have been reported to be associated with lower socioeconomic status (Jain and Choi, 2015). Additionally, higher serum and urine concentrations of Cs have been reported in persons with higher socioeconomic status (Tyrrell et al., 2013).

4.4. Strengths and limitations

The current study aimed to determine trace element concentrations in the general population in the Nord-Trøndelag region, Norway. We based our work on the well characterized population in the HUNT3 Survey, which is a major strength of this study. The HUNT Study is a unique database with information on a wide range of data obtained through questionnaires, biological measurements, and interviews, with a large sample size and high attendance rates. This makes HUNT an excellent source for studying trace element concentrations in the general population. By applying a sex-, age-, and area-stratified probability sampling design, we obtained a sample highly representative of the population. We identified variations in trace element concentrations with socio-demographic and lifestyle factors, statistically significant also after stringent correction for multiple testing and adjusted for potential confounding factors.

The Bonferroni method for correcting for multiple testing (applied in this study) is a conservative method, and we recognize that our study may not have sufficient statistical power to reveal minor differences between subgroups in the population. Although the HUNT Study contains detailed information on its participants, future studies should aim to include more details regarding dietary habits (including seafood intake and game meat consumption), information on drinking water and regional geochemical data, and clinical chemistry measurements (e.g., hematocrit and transferrin), to better adjust for these factors. This could provide a deeper understanding of some of the observed associations found in this study. Although our results suggest trace element concentrations to vary with lifestyle and socio-demographic factors, we emphasize that these results do not necessarily imply causality.

Whole blood is an excellent sample material for a broad range of trace elements, but we recognize that other sample materials are better suited for some trace elements (Gil and Hernández, 2015). Future studies could therefore include urine, serum, plasma, or tissue samples to provide complementary biological information on trace element status and for a better assessment of body burden. Additionally, information on trace element speciation is important to evaluate the potential biological effects of some trace elements. In the current study, we aimed to minimize the potential contamination from the stainless-steel needles by collecting the sample for trace element analysis as the last sample tube. However, some residual contamination may still be present influencing some of the reported concentrations, particularly Cr and Ni.

5. Conclusions

In this large population-based study, we report whole blood concentrations of 28 trace elements in the general population of the Nord-Trøndelag region, Norway. Trace element concentrations were generally comparable to those reported in other recent studies and suggest a low exposure to toxic trace elements for the residents in the region. We found differences in trace element concentrations between the geographical areas for As, B, Br, Ca, Cs, Ga, Au, Fe, Pb, Mg, Mn, Hg, Mo, Rb, Se, Ag, Tl, Sn and Zn, and for the participants' lifestyle and socio-demographic characteristics, particularly sex (B, Cd, Ca, Cu, Ga, Fe, Pb, Mg, Rb, and Zn), age (B, Cd, Cs, Au, Fe, Pb, Hg, Rb, Se, Ag, Sr, and Zn), smoking (Cd and Rb), and alcohol intake (B, Cs, and Pb). These differences were statistically significant after adjustment for potential

confounders and almost all differences were still significant after using a stringent threshold correction for multiple testing. Our study demonstrates the importance of considering these factors when evaluating levels of trace elements in the general population.

CRediT authorship contribution statement

AS: Methodology, Investigation, Formal analysis, Writing - Original Draft, and Writing - Review & Editing, AFH: Methodology, Investigation, Formal analysis, Writing - Original Draft, and Writing - Review & Editing. AS and AFH contributed equally. TS: Methodology, Writing - Review & Editing, and Supervision, SL: Methodology, Investigation, and Writing - Review & Editing, TMC: Methodology, and Writing - Review & Editing, PRR: Methodology, Formal analysis, and Writing - Review & Editing, KM: Methodology, Writing - Review & Editing, and Supervision, BOÅ: Methodology, Formal analysis, Writing - Review & Editing, and Supervision, TPF: Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing, Supervision, and Funding acquisition.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2021.150875.

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