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The Northern Norway Mother-and-Child Contaminant Cohort (MISA) Study: PCA analyses of environmental contaminants in maternal sera and dietary intake in early pregnancy☆

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ABSTRACT

Background: Although predictors of contaminants in serum or whole blood are usually examined by chemical groups (e.g., POPs, toxic and/or essential elements; dietary sources), principal component analysis (PCA) permits consideration of both individual substances and combined variables.
Objectives: Our study had two primary objectives: (i) Characterize the sources and predictors of a suite of eight PCBs, four organochlorine (OC) pesticides, five essential and five toxic elements in serum and/or whole blood of pregnant women recruited as part of the Mother-and-Child Contaminant Cohort Study conducted in Northern Norway (The MISA study); and (ii) determine the influence of personal and social characteristics on both dietary and contaminant factors.
Methods: Recruitment and sampling started in May 2007 and continued for the next 31 months until December 2009. Blood/serum samples were collected during the 2nd trimester (mean: 18.2 weeks, range 9.0–36.0). A validated questionnaire was administered to obtain personal information. The samples were analysed by established laboratories employing verified methods and reference standards. PCA involved Varimax rotation, and significant predictors ($p \leq 0.05$) in linear regression models were included in the multivariable linear regression analysis.
Results: When considering all the contaminants, three prominent PCA axes stood out with prominent loadings of: all POPs; arsenic, selenium and mercury; and cadmium and lead. Respectively, in the multivariate models the following were predictors: maternal age, parity and consumption of freshwater fish and land-based wild animals; marine fish; cigarette smoking, dietary PCA axes reflecting consumption of grains and cereals, and food items involving hunting. PCA of only the POPs separated them into two axes that, in terms of recently published findings, could be understood to reflect longitudinal trends and their relative contributions to summed POPs.
Conclusions: The linear combinations of variables generated by PCA identified prominent dietary sources of OC groups and of prominent toxic elements and highlighted the importance of maternal characteristics.

Introduction

Contaminants occur or are released into nature and will eventually enter the food chain making this a primary route for human exposure (AMAP, 2009). Prominent environmental pollutants in the human body include persistent organic pollutants (POPs) and toxic elements and are detected in biological samples in varying quantities (AMAP, 2009). Although predictors of concentrations of contaminants in serum or whole blood of pregnant women

☆ The Norwegian title of the project is: Miljøgifter i svangerskapet og i ammeperioden (MISA).

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are usually studied by chemical groups (e.g., POPs, toxic and/or essential elements), principal component analysis (PCA) permits consideration of both individual and combined groups. The same strategy can also be applied to dietary sources. This approach is pursued in the current paper and involves dietary information and suites of contaminants including: eight PCBs, four OC pesticides, five essential elements—copper (Cu), manganese (Mn), molybdenum (Mo), selenium (Se) and zinc (Zn)—and five toxic elements namely arsenic (As), cadmium (Cd), cobalt (Co), mercury (Hg) and lead (Pb).

Most, but not all, studies investigating dietary intake in relation to concentrations of environmental contaminants in biological specimen include environmental contaminants as single predictors. Birgisdóttir et al. (2013) found that seafood intake was associated with a PCA-generated factor that included iodine (I), Se, As and Hg. Similarly, Kvalem et al. (2009) observed four distinct food factors linking intake of fish liver and seagull eggs to blood concentrations of dioxins and PCBs. PCA was used by Odland et al. (2001) to group human placental concentrations of 11 essential and 5 toxic elements. Factor 1 explained 35.3% of the total variation and featured high loadings of phosphorus (P), calcium (Ca), magnesium (Mg), barium (Ba), strontium (Sr), Pb, and nickel (Ni). The metals in this group all form insoluble phosphates and, based on its associations with smoking and gestational age, this grouping could be interpreted to reflect placental mineralization. These examples clearly illustrate that PCA is a powerful statistical tool in biomonitoring.

Intake of fish and marine mammals are well known predictors of the presence of POPs in human tissues (Kvalem et al., 2012; Caspersen et al., 2013), as are sociodemographic variables like age, parity and educational achievement (Hansen et al., 2010). Inorganic Hg is converted by microorganisms to the methyl Hg (Me – Hg) form that accumulates in the aquatic food chain (Moyer, 2012). Consequently, seafood consumption as well as living in coastal municipalities have been shown to be significant predictors of blood Hg concentrations (Jenssen et al., 2012). Nevertheless, Golding et al. (2013) found seafood explained only 8.8% of the total variation in blood Hg concentrations.

It is well known that smoking is the primary source of Cd, and low iron (Fe)-stores are known to be inversely related to Cd blood concentrations among non-smoking women (Charania et al., 2014; Gallagher et al., 2011; Meltzer et al., 2010; Vahter et al., 2007). Cd concentrations vary in foods, but fibre-rich foods like cereals (especially rice), vegetables and shellfish contribute to Cd intake (Vahter et al., 2007; Birgisdóttir et al., 2013). Bjermo et al. (2013) have demonstrated meat intake to be inversely related to blood Cd concentrations. Smoking also contributes to increased blood Pb concentrations (Chelchowska et al., 2013; Taylor et al., 2013), and its uptake is found to be inversely related to Fe-stores (Mahaffey, 1990). Exposure of the general population to Pb has been linked to multiple sources including: dietary (e.g., consumption of foods grown on contaminated soils, some wines, hunted game and waterfowl and the associated use of leaded ammunition); leaded paints; contaminated soils and air; and certain hobbies such as making Pb sinkers (Nieboer et al., 2013; Meltzer et al., 2013; Hanning et al., 2003). Cereals (rice, grains and thus flour) and certain vegetables and legumes (especially carrots and peas) are good sources of inorganic As (iAs), which constitutes the toxic form of this element (Schoof et al., 1999). Non-toxic organic As occurs in meat and cereals and especially in seafood, ranging 160 ng/g in freshwater fish to 2360 ng/g in saltwater fish (Schoof et al., 1999).

The diet constitutes the primary source of Co and Ni (Shenkin and Roberts, 2012; Moyer, 2012; Barceloux, 1999a,b). Of these, Ni is the most common as it is an important component of stainless steel (chromium being the other). Contact with stainless steel appliances and resulting intake by hand-to-mouth activity seems a plausible source of Ni especially for children, and it can also be present in drinking water when taps are not flushed before drinking (Ni is a common component of faucets). Neither Ni nor Co have essential functions in humans, although diet-derived vitamin B12 contains Co. Low Fe status also promotes the uptake of Co (Meltzer et al., 2010).

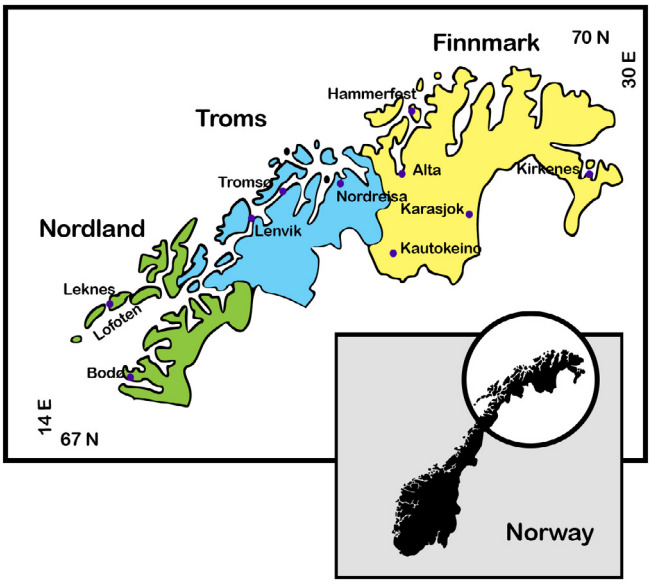

Fig. 1. Map of the Northern Norway study area.

Zn, Cu, Mn, Mo and Se are essential elements that are required for good health and are taken in through the diet. Zn is present in all types of food, with high protein items representing prominent sources (Shenkin and Roberts, 2012; Barceloux, 1999c). By contrast, meats and dairy products are poor in Cu, while mushrooms, dried fruits, legumes, whole-cereal grain products, peanut butter, nuts, organ meats (liver), and shellfish (crustaceans, oysters) have relatively high contents (Shenkin and Roberts, 2012; Barceloux, 1999d). Sources of Mn also include whole grain foods, nuts, leafy vegetables, as well as soy products and teas (Shenkin and Roberts, 2012; Barceloux, 1999e). Cereals (rice, grains, especially flour) and certain vegetables, legumes (especially peas and beans) also have high Mo content (Shenkin and Roberts, 2012; Barceloux, 1999f). And finally, wheat, cereal products and especially fish are good providers of Se (Brantsaeter et al., 2010).

The aims of this study were fourfold: (i) characterize the sources and predictors of the AMAP's suite of persistent organic pollutants, toxic and essential elements in serum and/or whole blood of pregnant women recruited as part of the Mother-and-Child Contaminant Cohort Study conducted in Northern Norway (The MISA study); (ii) compare the explanatory impact of using single *versus* PCA-generated dietary intake variables and of single contaminant groups *versus* combining them; and (iii), determine what influence personal and social characteristics had on both dietary and contaminant factors.

Material and methods

Description of Geographical area and recruitment

The recruitment and sampling for the MISA project started in May 2007 and continued for the next 31 months, until December 2009. Pregnant women from the three northern-most counties of Norway, namely Finnmark, Troms and Nordland (Fig. 1), were invited to participate in the study when making their first ultrasound appointment at antenatal centres. All women received a

letter of invitation describing in layman's terms the details of the study: its objectives; the physical, chemical and biological tests/examinations to be conducted; project finances; and ethical approval details. Enrolment was confirmed after written consent was received. The objective was to enrol the women before they reached gestational week 20. A total of 2600 women were invited to participate, 609 responded of whom 52 avoided further contact. The remaining 557 women received a project package, including a questionnaire and a biological sampling kit. Of these, 15 did not donate blood and 27 did not hand in the written consent form, thereby failing the inclusion criteria. This left 515 eligible study subjects. Additional details are provided in Veyhe et al. (2012).

Sampling

Full details of the specimen sampling and other procedures were provided previously (Veyhe et al., 2012). In short, at inclusion participants donated blood and urine samples, their blood pressure was measured and body weight assessed (wearing light clothes and measured to the nearest kg); and self-reported height (verified against that in the medical record). Optimally, this procedure was repeated three days and 6 weeks postpartum. At delivery, blood pressure and body weight were measured and a maternal hair sample was also obtained.

Questionnaire

The food frequency questionnaire (FFQ) was described earlier (Veyhe et al., 2012). Briefly, the questionnaire was divided into two parts. Part one pertained to personal information, such as lifetime residency (including municipality), education and work histories, household income, ethnic affiliations and marital status. Part two provided information about tobacco and alcohol use, and food consumption details for the past year. The FFQ was adapted from NOWAC, the Norwegian Women and Cancer Study (Hjartåker et al., 2007), although with expanded details of fish intake, including lifetime seafood intake (i.e., childhood, youth and in adult life). Intake of fish oil products, vitamins and other supplements were also asked for. The dietary information was converted from amount and frequency to daily intake in grams per day using a standardized measurement table (Blaker's Norwegian Weight and Measurement Table; Blaker and Aarsland, 1995). Daily energy and nutrient intakes were calculated using The Norwegian Food Composition Database 2006 (Matportalen, 2014).

Blood sample collection

Blood/serum samples were collected during the 2nd trimester (mean of 18.2 weeks and range 9.0 – 36.0). The blood was drawn from the antecubital vein into BD Vacutainers. The serum samples tubes (SST II Plus Avance 10/8.5 ml) were centrifuged at 2000 RCF for 10 min. For the whole blood tubes the details are: HemogardTM/Royal Blue, Ref# 368381, plastic, 6 mL, with 10.8 mg K_2 EDTA (Becton Dickinson, Plymouth, UK). The vacutainers were transported to the University of Tromsø, where the serum was transferred into glass vials pre-rinsed with *n*-hexane/acetone and whole blood to 4.5 mL cryo-vials. Samples were stored at −20 °C until analysis.

Analytical methodology

Serum sample preparation

Serum samples were analysed at the Norwegian Institute for Air Research's (NILU) laboratory in Tromsø Norway. The extraction and clean-up procedures for the POPs have been described by Hansen et al. (2010). Briefly, serum samples were extracted in an Oasis HLB solid phase extraction (SPE) column (540 mg of sorbent; Waters Corp., Milford, MA, USA) and were cleaned up using Florisil columns.

Lipid determination

As reported previously (Veyhe et al., 2013) lipids in serum were determined enzymatically and the amount in each sample was calculated using the following summation formula: TL = 1.677 (TC – FC) + FC + TG + PL, where TL = total lipids, TC = total cholesterol, FC = free cholesterol, TG = triglycerides and PL = phospholipids.

Analysis of sera and QA/QC

Instrumental details for the measurements of PCBs and pesticides are provided in Hansen et al. (2010). Briefly, the extracts were analysed using an Agilent 7890A gas chromatograph (GC), equipped with a 5975c mass spectrometer (Agilent Technologies, Böblingen, Germany). The GC was fitted with a 30 m DB5-MS column (0.25 mm id and 0.25 μm film thickness; J&W, Folsom, USA), with helium (6.0 quality, Hydrogas, Porsgrunn, Norway) as the carrier gas. Two μl of the sample extract were injected in the splitless mode using a split/splitless injector (injector and autosampler–Agilent 7683 Series, Agilent Technologies, Böblingen, Germany). The selected ion monitoring (SIM) mode was used for both electron capture dissociation and impact ionization.

The NILU Laboratory participates in the international AMAP Human Health ring test for Persistent Organic Pollutants (POPs) in human serum from this programme's outset and to date has performed well (within ± 20% of assigned values). Also, summed lipid concentrations in test samples ($n = 10$) were within a 15% deviation from assigned values. [AMAP ring test results are available from the Laboratoire de toxicology, Institut national de santé publique du Québec (INSPQ, 2014).]

A blank and a SRM (Standard Reference Material® 1958, Organic Contaminants in Fortifed Human Serum; National Institute of Standards and Technology, Gaithersburg, MD, USA) were analysed for every 10 samples measured to quantify laboratory-derived sample contamination and the accuracy of the method. Internal standard mixtures contained 29 different ^{13}C-labelled OCs. The limits of detection (LODs) were calculated as three times the area of the chromatogram noise or the average concentrations found in blank samples. The average recoveries of the internal standards varied between 60% and 97%.

Whole blood sample preparation

All analytical work involving whole blood samples was carried out at the National Institute of Occupational Health (NIOH), Oslo, Norway. To 1.0 mL of whole blood in an acid-precleaned polypropylene digestion tube, 1.5 mL of 65% ultrapure nitric acid (Chemscan Ltd., Elverum, Norway) was added. After heating in a laboratory oven at 90 °C for 1 h, the digest was cooled to room temperature and 200 μL of an internal standard solution was added containing ^{72}Ge for ^{75}As and ^{77,78,82}Se; ^{115}In for ^{98}Mo and ^{114}Cd; ^{205}Tl for ^{206,207,208}Pb and ^{200,201,202}Hg; ^{60}Ni for ^{55}Mn, ^{59}Co, ^{63,65}Cu and ^{64,66,68}Zn; and was subsequently diluted to a final volume of 10 mL with ultrapure water. Further details are provided by Hansen et al. (2011).

Analysis of whole blood and QA/QC

Details for the measurements of selected elements are outlined in Hansen et al. (2011). In brief, maternal whole blood was analysed

for As, Cd, Co, Cu, Hg, Mn, Mo, Pb, Se and Zn by inductively plasma-mass spectrometry (ICPMS), employing a high resolution magnetic sector field Element 2 mass spectrometer (Thermo Electron, Bremen, Germany) calibrated with whole-blood matched standard solutions. Routine acid leaching of all vessels and use of ultrapure water and nitric acid assured that the blank samples were as low as possible in order to obtain adequate limits of detection (LOD) (three times the standard deviation for blank samples). One aliquot of each blood sample was analysed in triplicate.

Seronorm human whole blood TM Trace Elements (Sero Ltd., Billingstad, Norway) quality control materials served as reference materials. After every 10 blood samples, a control sample at two different concentrations was analysed.

The NIOH laboratory participates in the Wadsworth Center, New York State (USA) Department of Health Proficiency Testing Schedules for trace elements in whole blood and urine, with acceptable results (typically within ± 2 – 10% deviation from the target values) and no indication of any systematic biases.

Statistical analysis

The statistical analyses were performed using the IBM SPSS Statistics for Windows (version 21.0; SPSS Inc., Chicago, IL, USA). All concentrations below the LOD were replaced with LOD/$\sqrt{2}$ as recommended by Eik Anda et al. (2007). For descriptive purposes, means and standard deviations are provided for continuous variables as well as the median and range. For categorical variables, the % in each category is reported. Normality of distributions was assessed by the Kolmogorov – Smirnov test. Neither the dietary variables nor the contaminant variables were normally distributed and to analyse differences between groups, the non-parametric Mann – Whitney Test was used. The ANOVA and/or the *Post Hoc* Bonferroni Test were employed for comparisons involving PCA-generated variables. The corresponding *P*-values are designated in the text respectively as: P_{MW}, P_A and P_B. Statistical significance was set at $P \leq 0.05$.

For variable dimension reduction, we used Principal Component Analysis (PCA) based on Eigenvalues >1 and Varimax rotation to produce a smaller number of uncorrelated variables while retaining most of the variance of the raw data. Lipid-adjusted serum concentrations of OCs, whole blood concentrations of elements, and grouped dietary intake variables were subjected to PCA analyses. For OCs, a detection frequency of <70% constituted the inclusion criterion. No such restriction was required for the elements (see Table S4).

In the univariable linear regression analyses, links were explored between contaminant variables and: maternal age, educational level and smoking habits in early pregnancy, parity, breastfeeding and pre-pregnancy BMI (pp-BMI), and between dietary variables and: maternal age, educational level, smoking in early pregnancy, and physical activity (from 1, indicating low activity, to 10 which equals very high activity level) prior to pregnancy were examined. Significant predictors ($p \leq 0.05$) from these linear regression models were included to generate multivariable linear regression models.

Ethical considerations

The study was approved by the Regional Committees for Medical and Health Research Ethics (REC North), as well as by the Norwegian Data Inspectorate. The women participated on a voluntary basis and, as indicated earlier, enrolment required receiving written consent.

Results

Study group characteristics

Sociodemographic and personal characteristics are presented in Table S1. The women on average were 30.6 years old with a range of 25 years (18 – 43 years). Over 40% had higher education (>16 years of schooling, which is equivalent to the length of a bachelor (BA) education with a median length of 16 years; 60% had a yearly household income over NOK 600,000; and the great majority were married or cohabited (95.5%) and of Norwegian ethnic affiliation (89.9%). Nearly 26% of the women reported smoking 6 months prior to pregnancy (not shown), which declined to almost 18% in early pregnancy and to 6.6% by termination. Only 8% reported to be teetotallers, but alcohol intake during pregnancy appears to have been modest: less than 5% reported any wine intake during pregnancy, and 1.6% reported having consumed beer. The majority (64%) of the women had pp-BMI values within the normal range (18.5 – 24.9 kg/m^2), 1.2% were underweight, 24.3% overweight and 10.4% obese (>30.0 kg/m^2), with an average value of 24.4 (see Table S1).

The majority (55.3%) of the participants lived in the county of Troms, with the remainder (see Table S1) divided between the counties of Finnmark (16.7%) and Nordland (28%). The women were asked to record all municipalities they had lived in. It was then decided whether the municipality was on the oceanfront, in a fjord or inland, and that the longest residence time determined whether a respondent was recorded as 'living on the coast', 'by the fjord' or 'inland'. Accordingly, nearly 56% lived on the coast, just under 31% by fjords and 5% inland (not shown). Altogether 91.7% reported habitation history.

About 60% of the women had at least one previous delivery. In current dataset of singleton pregnancies, 3.4% delivered before gestational week 37 and 9 (1.8%) infants were born with a birth weight below 2500 g (see Table S1), of whom three had a gestational age <37 weeks and 24 (4.9%) were large for gestational age (LGA) [ICD-10 classification P08.0; WHO, 2010]. Nine sets of twins were included in the cohort; they were delivered between gestational week 27 – 38 (mean 35.2 weeks), with a mean birth weight of 2257 g (range: 830 – 3070 g). The vast majority of mothers with previous deliveries ($n = 298$) reported ever breastfeeding ($n = 228$), 10 only breastfeeding with additional supplements, and four never breastfed. Breastfeeding information was not provided by 70 of the mothers.

Major findings

Dietary issues

Daily dietary intake in terms of energy and macro- and micronutrients is presented in Supplementary Table S2. The distribution of the daily energy intake from major food components was 17% (protein), 46% (carbohydrates) and 34% (fat). In terms of dietary supplements and folic acid, 47% and 71% respectively reported daily intake during pregnancy. For fish oil products, 66% recorded an intake once a week or more during the winter season. This fell to 52% in other seasons (not shown). Seven subjects failed to submit the FFQ despite reminders, and 12 were incomplete and thus were not included in the dietary calculations.

Concentrations of OCs and elements

Concentrations of wet-weight and lipid-adjusted POPs in serum are presented in Table 1, and limits of detection (LODs) in Supplementary Table S3. The highest average concentrations were found for *p,p′*-DDE and, relative to it, in declining order: PCB 153 > 180 > 138 > HCB > PCB 170 > 187 > 118 >163 > *trans*-Nonachlor > PCB 156 > 99 > 183 > *cis*-Nonachlor. Detection frequencies for the pesticides were ≥96% and for eight of the 12 PCBs ≥81%. PCB 101, 156,

Table 1
Wet-weight and lipid-adjusted concentrations (pg g^{-1}) of PCBs and pesticides in serum of pregnant (early pregnancy) women from Northern Norway.

Compound[a]	Wet-weight levels (pg g^{-1} serum)					Lipid-adjusted levels (ng g^{-1} lipids)			
	n[b]	AM[c]	SD[d]	GM[e]	Min – max[f]	AM[c]	SD[d]	GM[e]	Min – max[f]
PCB 99	507	16.5	10.6	14.2	3.5 – 133	2.5	1.5	2.2	0.4 – 18.1
PCB 118	508	31.1	20.6	26.5	7.1 – 228	4.8	3.2	4.1	1.0 – 38.3
PCB 138	508	110	69.6	96.4	15.8 – 860	16.9	10.2	14.9	2.8 – 118
PCB 163	501	26.2	17.2	22.3	5.7 – 181	4.0	2.5	3.4	0.7 – 24.6
PCB 153	508	184	120	161	25.5 – 1470	28.2	17.4	24.8	5.3 – 201
PCB 156[g]	499	17.3	12.2	15.0	*LOD – 192*	2.7	1.8	2.3	*LOD – 26.3*
PCB 170	508	48.1	32.1	41.5	5.7 – 434	7.4	4.6	6.4	1.0 – 59.2
PCB 180	508	123	84.3	107	16.8 – 1160	18.9	12.4	16.5	3.0 – 159
PCB 183[g]	494	11.6	9.7	9.8	*LOD – 151*	1.8	1.4	1.5	*LOD – 20.6*
PCB 187	502	32.5	20.7	28.0	3.8 – 216	5.0	3.0	4.3	0.8 – 29.5
p,p'-DDE	508	291	216	251	56.5 – 2440	44.9	32.9	38.7	10.9 – 351
HCB	507	67.6	31.6	62.2	21.2 – 317	10.3	4.4	9.6	3.5 – 53.3
trans-Nonachlor	508	21.8	15.0	17.9	3.6 – 129	3.3	2.2	2.8	0.6 – 17.6
cis-Nonachlor	507	5.2	4.0	4.0	0.4 – 33.3	0.8	0.6	0.6	0.1 – 4.5

[a] PCB(s), polychlorinated biphenyl(s); p,p'-DDE, dichlorodiphenyldichloroethylene; HCB, hexachlorobenzene. Average values are presented only for compounds with detection frequencies ≥70% (but see footnote 'g'); all levels below the LOD were set to LOD/$\sqrt{2}$.
[b] The number of participants (n) varied because the observed ion-mass ratios were unacceptable.
[c] AM = Arithmetic mean.
[d] SD = Standard deviation.
[e] GM = Geometric mean.
[f] Ranges are given as minimum to maximum or LOD to maximum.
[g] Detection frequency: 50 – 69%.

183 and 194 were omitted from further analysis as the detection frequency was <70% (the criterion for inclusion).

Table 2 summarizes concentrations for five essential and five toxic elements in whole blood. For 7 of the 10 elements (Cd, Pb, Cu, Mn, Mo, Se, and Zn) the % detected was 100%, and for the others (As, Co, and Hg) it was ≥98.2% (see Supplementary Table S4). The elements were measured in two rounds, with the first set consisting of 211 samples as reported by Hansen et al. (2011); the second batch of 71 was measured subsequently. Since the LODs for the first round were more conservative (slightly higher values) for all ten elements, these were adopted for the present study and are reported in Supplementary Table S4.

A comparison of means between the first and second rounds revealed some differences for Cu (P_{MW} < 0.001), Mo (P_{MW} < 0.001) and Zn (P_{MW} = 0.002). But the observed relative concentration patterns remained the same as presented earlier by Hansen et al. (2011): for the toxic elements the highest concentrations were again found for Pb, followed by As > Hg > Cd (smoker) > Cd (non-smoker) > Co, with the relative concentrations of the essential elements exhibiting the pattern Zn > Cu ⋙ Se ≫ Mn ≫ Mo.

Principal component analyses of POPs, elements and dietary habits

In the PCA with all contaminants (POPs and elements), six distinct factors reflected 74% of the total variance (Table 3, Model 1). All of the POPs appear in the first PC variable, and it explains 41.5% of the variation. Based on the relatively high loadings of POPs, it is designated as the 'POPs axis'. The elements group on the remaining five PCA factors (PC-2 – PC-6) and explained from 9.3% to 5.6% of the total variation. Based upon the substantive loadings indicated in bold type in Model 1 (All contaminants), PC-2 can be described as an 'arsenic/mercury/selenium' axis; PC-3 a 'cobalt/manganese' axis; PC-4 a 'copper/molybdenum' axis; PC-5 a 'zinc' axis; and PC-6 a 'cadmium/lead' axis. Since the elemental chemical analysis was limited to 282 samples, the PCA of POPs was conducted separately on all available results to increase the statistical power (N = 498). The findings are summarized in Table 3 (Model 2). Two primary factors were evident that explained 83.3% of total variation (Model 2, Table 3). PC-1 features *p,p'*-DDE and all PCBs but PCB 118, while PC-2 includes the pesticides and PCB 118. When considering the elements alone (Model 3, Table 3), the corresponding loadings of PC-1 – PC-5 accounted for 68.7% of the variation, and resembled

Table 2
Whole blood concentrations of toxic and essential elements in pregnant women (early pregnancy) from Northern Norway.

	Elements[a]	Concentrations (Wt L^{-1})	n[b]	AM[c]	SD[d]	GM[e]	Min – max
Toxic	As	µg	282	2.09	2.08	1.46	0.14 – 12.8
	Cd	µg	282	0.23	0.26	0.18	0.04 – 2.74
	Co	µg	282	0.13	0.11	0.10	0.02 – 0.60
	Hg	µg	282	1.51	1.02	1.21	0.10 – 6.64
	Pb	µg	280	8.02	3.25	7.44	2.22 – 25.8
Essential	Cu	mg	282	1.64	0.26	1.62	1.00 – 2.87
	Mn	µg	282	11.1	3.73	10.6	3.79 – 37.8
	Mo	µg	282	0.74	0.26	0.70	0.24 – 2.28
	Se	µg	281	85.8	13.6	84.7	58.17 – 128
	Zn	mg	282	5.27	0.84	5.20	2.73 – 9.85

[a] As, arsenic; Cd, cadmium; Co, cobalt; Hg, mercury; Pb, lead; Cu, copper; Mn, manganese; Mo, molybdenum; Se, Selenium; Zn, zinc.
[b] The variation in number of participants is due to the exclusion of extreme values.
[c] AM = Arithmetic mean.
[d] SD = Standard deviation.
[e] GM = Geometric mean.

Table 3
Principal Component Analysis (PCA) scores of POPs (lipid adjusted) and elements presented in three models; all contaminants (Model 1), POPs only (Model 2) and elements only (Model 3) in maternal serum (mean gestational age of 18.2 weeks)[a,b].

All contaminants[c]	Model 1 (All contaminants) $n = 266$						Model 2 (POPs only)[d] $n = 498$		Model 3 (Elements only) $n = 279$				
	PC-1 (41.5%)	PC-2 (9.3%)	PC-3 (6.2%)	PC-4 (6.0%)	PC-5 (5.7%)	PC-6 (5.6%)	PC-1 (50.4%)	PC-2 (32.9%)	PC-1 (19.1%)	PC-2 (13.5%)	PC-3 (12.4%)	PC-4 (12.1%)	PC-5 (11.6%)
PCB 99	**0.892**	0.128	−0.019	0.098	0.048	−0.026	**0.692**	0.573					
PCB 118	**0.861**	0.093	−0.045	0.113	0.062	−0.004	0.552	**0.666**					
PCB 138	**0.962**	0.080	0.001	−0.052	0.029	−0.045	**0.825**	0.480					
PCB 163	**0.894**	0.120	−0.032	0.024	−0.070	−0.002	**0.768**	0.452					
PCB 153	**0.975**	0.090	−0.005	−0.089	0.000	−0.034	**0.875**	0.448					
PCB 170	**0.879**	0.007	0.022	−0.176	−0.097	0.032	**0.890**	0.297					
PCB 180	**0.915**	0.072	0.034	−0.185	−0.041	−0.024	**0.897**	0.331					
PCB 187	**0.949**	0.076	0.042	−0.087	−0.014	−0.011	**0.862**	0.435					
p,p'-DDE	**0.700**	0.046	0.101	−0.014	0.087	−0.212	**0.706**	0.222					
HCB	**0.813**	0.047	−0.117	0.060	0.039	0.030	0.464	**0.682**					
trans-NC[e]	**0.767**	0.288	−0.077	0.321	−0.048	−0.017	0.337	**0.889**					
cis-NC[e]	**0.719**	0.324	−0.106	0.371	−0.041	0.006	0.251	**0.920**					
As	0.042	**0.838**	0.007	−0.038	−0.099	0.066			**0.799**	0.054	0.017	−0.137	−0.014
Cd	−0.105	−0.032	0.177	0.008	−0.106	**0.778**			−0.087	0.180	**0.795**	−0.171	−0.054
Co	−0.080	0.159	**0.802**	−0.049	−0.141	0.138			0.111	**0.813**	0.133	−0.113	−0.046
Cu	−0.036	−0.118	0.089	**0.761**	0.025	−0.196			−0.107	0.108	−0.227	0.031	**0.742**
Pb	0.036	0.022	0.003	0.029	0.482	**0.662**			0.057	−0.016	**0.695**	0.422	0.059
Mn	0.039	−0.077	**0.795**	0.135	0.257	0.047			−0.035	**0.792**	0.020	0.236	0.115
Hg	0.240	**0.787**	0.055	−0.025	0.028	0.001			**0.836**	0.029	0.017	−0.012	−0.026
Mo	−0.005	0.033	−0.003	**0.596**	−0.130	0.215			0.076	−0.043	0.207	−0.119	**0.759**
Se	0.227	**0.649**	0.048	−0.004	0.413	−0.173			**0.728**	−0.005	−0.101	0.376	0.014
Zn	−0.075	0.039	0.065	−0.122	**0.829**	0.040			0.019	0.091	0.036	**0.868**	−0.096

[a] The PCA is based on Eigenvalues >1 and Varimax rotation.
[b] Highlighted scores (also called loadings) indicate that the variance in the corresponding element items contribute substantially to the variance summarized by that principal component (PC).
[c] See footnote 'a' of Tables 1 and 2 for full names.
[d] When the PCA analysis was based on wet-weight contaminant levels, only one factor describing 76% of the variation resulted.
[e] NC, Nonachlor.

Table 4
PCA scores of 20 food groups derived from FFQ recorded in early pregnancy (mean gestational age of 18.2 weeks; $n = 496$) representing last 12 month's intake[a,b].

Food groups	PC-1 (9.4%)	PC-2 (8.0%)	PC-3 (7.9%)	PC-4 (7.8%)	PC-5 (7.4%)	PC-6 (6.6%)	PC-7 (5.8%)	PC-8 (5.1%)
Fruit	**0.650**	0.251	−0.018	0.121	−0.160	−0.166	−0.153	−0.205
Berries	**0.617**	−0.035	0.344	−0.057	0.148	−0.018	−0.069	−0.179
Soup	**0.579**	−0.007	0.032	−0.004	0.029	0.046	0.149	0.133
Coffee and tea	**0.554**	−0.044	−0.251	0.141	0.199	0.054	0.194	0.221
Vegetables	**0.523**	0.439	−0.149	0.096	−0.145	0.296	−0.104	−0.003
Marine lean fish and shellfish	−0.004	**0.769**	−0.035	0.074	−0.083	0.166	0.062	−0.056
Marine fatty fish	0.127	**0.736**	0.001	0.014	0.162	−0.002	0.007	0.183
Salty snacks and chocolate	0.057	0.087	**0.682**	0.104	−0.128	0.051	−0.070	0.229
Dessert	0.262	0.015	**0.642**	0.132	0.120	0.083	0.126	−0.128
Soft drinks and jam	−0.187	−0.143	**0.611**	−0.110	0.010	0.035	0.013	0.048
Grains and cereals	0.295	−0.007	0.067	**0.713**	0.082	0.123	−0.077	0.071
Fat on bread and with fish, mayonnaise	−0.096	0.038	0.051	**0.682**	0.141	0.009	−0.134	0.090
Milk and milk products, and rice porridge	−0.043	−0.006	0.014	**0.538**	−0.243	−0.207	0.409	−0.195
Pasta, potatoes and rice	0.055	0.139	−0.016	0.462	−0.028	0.263	0.122	0.054
Freshwater fish	0.017	0.115	−0.037	0.014	**0.785**	−0.040	0.003	0.024
Reindeer, reindeer products, moose and grouse	0.058	−0.043	0.038	0.083	**0.779**	0.127	0.013	−0.064
Sauce	0.068	0.095	0.017	0.061	0.082	**0.842**	0.072	−0.052
Meat and meat products	−0.090	0.067	0.418	0.203	0.026	**0.588**	−0.048	0.015
Whale and seal	0.111	0.005	−0.009	−0.080	−0.027	0.125	**0.790**	0.131
Fish liver	-0.063	0.452	0.087	0.079	0.238	−0.119	**0.500**	−0.118
Seagull eggs	0.015	0.072	0.122	0.117	−0.044	−0.047	0.058	**0.854**

[a] The PCA is based on Eigenvalues >1 and Varimax rotation.
[b] Highlighted scores (also called) loadings indicate that the variance in the corresponding element items contribute substantially to the variance summarised by the principal component (PC).

axes PC-2 – PC-6 of Model 1 (but note the shift in sequence of the axes).

To reduce the number dietary variables, summary variables combining several related food frequency variables were generated for use in the PCA (see Table 4). The eight primary axes shown explained 58% of the variation, with individual axes contributing from 9.4% to 5.1% of the total variance. To reflect their loadings, the following short-hand labels were adopted for the eight axes: PC-1 ('fruit & vegetables'); PC-2 ('marine fish'); PC-3 ('junk food'); PC-4 ('grains & dairy'); PC-5 ('local traditional food'); PC-6 ('sauce & meat'); PC-7 ('whale/seal & fish liver'); and PC-8 ('seagull eggs').

Relationships between food consumption and personal characteristics (post hoc tests)

Overall maternal age and education associated positively with the individual dietary factor scores PC-1('fruit & vegetables'), while for PC-3('junk food)' a negative trend was evident ($P_A \leq 0.05$). Education (years at school grouped by age: <13 years, 13 – 16 years, and >16 years) showed increasing trends for PC-1(Diet) ($P_A = 0.03$) and PC-4(Diet) ($P_A = 0.08$); it was negative for PC-3(Diet) ($P_A = 0.004$).

For smoking a negative trend was observed for PC-1('fruit & vegetables'), while it was positive for PC-3('junk food'), PC-7('whale/seal & fish liver') and PC-8('seagull eggs') ($P_A \leq 0.05$). No consistent patterns were observed for associations with physical activity and pp-BMI, except for a negative trend for PC-1('fruit & vegetables') with pp-BMI ($P_A = 0.03$).

Intake of game and freshwater fish was significantly ($P_B < 0.001$) higher among women living inland (intakes in g/day of 22 and 3 g/day of game and freshwater fish, respectively), than among those living by the coast (2.4 g/day and 0.5 g/day, respectively) or by fjords (3 and 1 g/day, respectively). For other food groups like meat, fruit, vegetables or milk products no distinct pattern between the geographical areas was found.

Women living inland had significantly higher factor scores for PC-1(All contaminants) than those residing on the coast ($P_B = 0.001$) or by fjords ($P_B = 0.03$). Comparable trends were found for PC-1(POPs only), PC-2(POPs only) and PC-6(All contaminants) (respectively, with P_A values of 0.04, 0.02 and 0.05); these differences did not reach significance for PC-2(All contaminants) ($P_A = 0.13$).

Since most of the dietary PC-factors have some dependence on maternal age, and the latter is a recognized predictor of plasma POPs, their relationships to contaminant PC-factors are dealt with in the multivariable regression modelling section.

Predictors of contaminant concentrations in serum

In the multivariable linear regression models (see Table 5) for PC-1(All contaminants), 37.6% of the variance was explained by maternal age, parity, freshwater fish and game intake. When fish liver was included into the model R^2 increased somewhat (38.4%), although the predictor variable itself was only roughly significant ($p = 0.08$). Maternal age, parity, pp-BMI and PC-2('marine fish') explained almost 20% of total variation of PC-1(POPs only). Replacement of PC-2('marine fish') in this model with the PC-8('seagull axis') slightly improved the overall fit (R^2 increased from 19% to 20%). PC-2(POPs only) was best explained by maternal age and breastfeeding along with dietary PC variables ($R^2 = 26.2\%$). PC-2(All contaminants) exhibited the best fit when the PC axes representing fruit & vegetables (PC-1) and seafood axes (PC-2 and PC-7) were included in the model ($R^2 = 24.2\%$). Based on β and R^2 values (see Table 5), the association of current smoking (contemporary with blood collection) was more robustly associated with PC-6 (All contaminants) compared to the consumption of grains and of traditional foods. Up to 42.6% of the variation was accounted for. No food variables or personal characteristic explained factors PC-3 to PC-5(All contaminants).

Discussion

Overview of multivariable linear regression models

Maternal age was a recurring positive explanatory variable in the multivariable linear regression models involving PC-contaminant axes (in 7 of the 12 models) and in two of three dietary models; see Table 5. For the same seven models, parity (substituted in one case by breastfeeding) constituted a negative predictor. These trends were also evident in our preliminary report of the incomplete MISA cohort (Hansen et al., 2010). The importance of these three predictors of OCs in maternal sera are well established, In cross-sectional studies, age is a positive predictor (Liberda et al.,

Table 5
Multivariable linear regression models: Significant predictors for selected factors from Table 3 Model 1 and Model 2 (Contaminant factors) and from Table 4 (Dietary factors).

	Predictors[a]	*B*	95% CI	*p*-Value	*β*	R^2
	PC-1 (All contaminants)					
1	Maternal age	0.11	0.09; 0.13	<0.001	0.52	0.376
n = 258	Parity	−0.40	−0.51; −0.29	<0.001	−0.38	
	Freshwater fish[b]	0.07	0.02; 0.12	0.004	0.17	
	Reindeer, innards, moose and grouse[b]	0.02	0.006; 0.03	0.004	0.17	
2	Maternal age	0.10	0.08; 0.13	<0.001	0.50	0.384
n = 258	Parity	−0.40	−0.51; −0.29	<0.001	−0.38	
	Freshwater fish[b]	0.07	0.02; 0.12	0.005	0.17	
	Reindeer, innards, moose and grouse[b]	0.02	0.005; 0.03	0.005	0.16	
	Fish-liver[a]	0.28	-0.04; 0.60	0.08	0.09	
	PC-1 (POPs only)					
1	Maternal age	0.09	0.07; 0.11	<0.001	0.42	0.189
n = 466	Parity	−0.26	−0.35; −0.14	<0.001	−0.24	
	pp-BMI[c]	−0.05	−0.06; −0.03	<0.001	−0.21	
	PC-2('marine fish')	−0.11	−0.19; −0.03	0.009	−0.11	
2	Maternal age	0.08	0.06; 0.10	<0.001	0.40	0.197
n = 466	Parity	−0.25	−0.35; −0.16	<0.001	−0.23	
	pp-BMI[c]	−0.05	−0.06; −0.03	<0.001	−0.21	
	PC-8('seagull eggs')	0.14	0.06; 0.22	0.001	0.14	
3	Maternal age	0.08	0.07; 0.10	<0.001	0.41	0.181
n = 475	Parity	−0.26	−0.35; −0.16	<0.001	−0.24	
	pp-BMI[c]	−0.04	−0.06; −0.03	<0.001	−0.20	
	PC-2 (POPs only)					
1	Maternal age	0.05	0.03; 0.07	<0.001	0.25	0.262
n = 418	Breastfeeding[d]	−0.60	−0.79; −0.41	<0.001	−0.29	
	PC-2('marine fish')	0.26	0.17; 0.35	<0.001	0.25	
	PC-5('local traditional food')	0.24	0.15; 0.32	<0.001	0.24	
	PC-7('whale/seal & fish liver')	0.18	0.10; 0.27	<0.001	0.18	
2	Maternal age	0.04	0.02; 0.06	<0.001	0.21	0.177
n = 483	Parity	−0.22	−0.32; −0.12	<0.001	−0.20	
	Freshwater fish[b]	0.06	0.03; 0.09	<0.001	0.16	
	Marine fatty fish[b]	0.02	0.01; 0.03	<0.001	0.19	
	Shellfish[b]	0.09	0.02; 0.16	0.01	0.11	
	PC-2 (All contaminants)					
1	Marine lean fish and shellfish[b]	0.01	0.005; 0.02	<0.001	0.22	0.196
n = 258	Marine fatty fish[b]	0.02	0.01; 0.04	<0.001	0.24	
	Whale and seal[b]	0.22	0.09; 0.35	0.001	0.19	
2	Marine lean fish and shellfish[b]	0.008	0.001; 0.01	0.02	0.15	0.227
n = 258	Marine fatty fish[b]	0.02	0.009; 0.03	0.001	0.21	
	Whale and seal[b]	0.23	0.10; 0.36	0.001	0.19	
	Vegetables[b]	0.002	0.001; 0.003	0.002	0.19	
3	PC-1('fruit & vegetables')	0.20	0.09; 0.32	0.001	0.19	0.242
n = 258	PC-2('marine fish')	0.37	0.27; 0.47	<0.001	0.38	
	PC-7('whale/seal & fish liver')	0.24	0.14; 0.34	<0.001	0.25	
	PC-6 (All contaminants)					
1	Years at school	−0.04	−0.07; 0.000	0.05	−0.10	0.426
n = 250	PC-4('grains & dairy')	0.18	0.09; 0.28	<0.001	0.19	
	PC-5('local traditional food')	0.12	0.03; 0.21	0.006	0.13	
	Present smoking[e] (Yes/No)	2.57	2.13; 3.00	<0.001	0.58	
2	Reindeer, innards, moose and grouse[b]	0.01	0.001; 0.02	0.03	0.11	0.388
n = 253	Grains and cereals[b]	0.001	0.000; 0.003	0.01	0.13	
	Present smoking[e] (Yes/No)	2.60	2.18; 3.02	<0.001	0.61	
	PC-1 Diet (Fruit & vegetables)					
n = 469	Maternal age	0.02	−0.001; 0.04	0.06	0.09	0.07
	Years at school	0.03	0.003; 0.06	0.03	0.10	
	pp-BMI[c]	−0.02	−0.04; −0.001	0.04	−0.10	
	Physical activity before pregnancy[f]	0.09	0.04; 0.14	<0.001	0.16	
	PC-2 Diet (Marine fish)					
n = 492	Maternal age	0.03	0.02; 0.05	<0.001	0.17	0.04
	Physical activity before pregnancy[f]	0.07	0.02; 0.13	0.005	0.13	
	PC-3 Diet (Junk food)[g]					
n = 471	Maternal age	−0.03	−0.05; −0.01	0.002	−0.15	0.06
	Years at school	−0.04	−0.08; −0.009	0.01	−0.12	
	pp-BMI[c]	0.02	−0.002; 0.04	0.08	0.08	

[a] For a summary of eligible personal information and dietary predictors, see Table S5 (i.e., those with significant *p*-values in the linear regression analyses).
[b] Dietary intake in g/day.
[c] BMI: Based on self-reported pre-pregnancy weight and height (pp-BMI).
[d] Breastfeeding (Yes/No).
[e] Present smoking (when filling in FFQ: mean gestational age 18.2 weeks (Yes/No)).
[f] Scale from 1 to 10.
[g] Analyses involving the dietary axes PC-4 and PC-8 showed no associations, and was limited to one variable for PC-5 (Years at school, $p = 0.04$), PC-6 (Years at school, $p = 0.05$) and PC-7 (pp-BMI, $p = 0.001$).

2014; Nøst et al., 2013; Bjerregaard et al., 2001; Rylander et al., 1997). By contrast, parity and life-time breastfeeding have a negative impact on circulating PCBs and OC pesticides (Polder et al., 2009; Rylander et al., 1997; Furberg et al., 2002). OCs are present in breast milk because of their lipid solubility (Polder et al., 2009; Ryan and Rawn, 2014; Mannetje et al., 2012), and parity constitutes a surrogate for life-time breastfeeding. In our study, parity appeared to explain more of the variability. This may well reflect the higher reporting of this parameter compared to breastfeeding.

Predictors of OCs

Considering the 'POPs only' group in the PCA analysis (Table 3), a clear separation of the PCBs plus *p,p′*-DDE (PC-1) from the OC pesticides plus PCB 118 (PC-2) occurs and a total variance explained is substantive (83.3%; PC-1 + PC-2). This delineation does not occur in Model 1 (All contaminants). The predictor variables retained for the PC-1('POPs only') axis are somewhat different than for PC-2('POPs only'). A plausible explanation is afforded by a recent analysis (Nøst et al., 2013) of POPs in Norwegian men followed from 1979 to 2007. The relative contributions to the sum of measured OC concentrations in serum were quite distinct for the OC pesticides plus PCB 118 [see PC-2 loading of Model 2 ('POPs only') in Table 3] compared to those with substantial loadings on PC-1 Model 2 ('POPs only'). For five separate measurements taken during the indicated timespan, Nøst et al. (2013) observed that the relative contributions of PCBs 180, 153, and 138/163 were substantial and increased with time; those of *p,p′*-DDE were considerable, although with a modest decreasing trend. By contrast, the proportion of the total serum OCs contributed by the prominent members of PC-2 Model 2 ('POPs only') was small throughout the 28-year observation period with a decreasing trend observed for HCB, a modest increase for *trans*-NC and a 'steady state' for PCB 118 (*cis*-NC was not included in the comparison). Most likely the PCA was responsive to this grouping of the relative contributions to the total OCs in our study. Indeed, and relatively speaking, the prominent members of the PC-2('POPs only') had lower concentrations than the prominent members of PC-1 ('POPs only') (see Table 1). A related perspective concerns a consideration of the mobilization of stored OCs in the study subjects. Hansen et al. (2010) showed that serum concentrations of OCs increased in parallel with circulating lipid concentrations known to be mobilized during pregnancy from fat tissues. Compared to the PC-2 ('POPs only') OCs, the mobilization of PC-1 ('POPs only') members from tissue stores might be expected to be more substantial relative to current intake than for members of PC-2('POPs only') group. The relatively stronger dependence of PC-2('POPs only') on current fish intake parameters (as daily intakes and most avidly when selecting the corresponding fish related diet PCA axes; see Table 5) is consistent with these various interpretations, as is the weaker influence of maternal age as a predictor (i.e., lower β values in the multivariable models).

The influence of pp-BMI for PC-1('POPs only') reflects the influence of body size and thus stored PCBs and *p,p′*-DDE. The dependence of OC concentrations on pp-BMI is uncertain as pointed out by Wolff et al. (2005, 2007), since positive and negative correlations, as well as none, have been reported for OCs. These authors demonstrated that BMI, weight change and time since peak exposures are key factors in the pharmacokinetics of individual OCs. The data in Table 5 indicate that in the present cohort the dependence of OCs on pp-BMI was negative and thereby reflects a "dilution" effect.

Magnitude of the observed OC concentrations in serum

The observed OC concentrations are comparable in magnitude to those reported by others for pregnant women in Nordic countries when considering the amount of fish consumption and the year of collection (Glynn et al., 2007; Halldorsson et al., 2008), but considerably lower than noted for women of reproductive age living in indigenous communities in northern areas of Canada. (Liberda et al., 2014; Butler Walker et al., 2003)

Predictors of elements

The elemental axes generated in Model 1 (All contaminants) were selected for the multivariable analyses because somewhat better fits were generally obtained and this enhanced our findings and conclusions.

Interestingly, the loadings of the five PCA axes representing the elements in Model 3 are of comparable magnitude to those identified in Model 1 (All contaminants). In fact, use of Model 3 (Elements only) in the multivariable analyses increased/decreased the total variation explained minimally. This supports our decision to use Model 1 in the multivariable analysis. Model PC-2 (All contaminants) indicates that As, Se and Hg have a unique dietary source, namely mainly of marine origin. This observation nicely illustrates that this triad of elements constitutes a recognized biomarker of fish consumption (Brantsaeter et al., 2010).

Cd and Pb contents also appeared to have unique predictors. It is well established that the primary source of Cd in the general population is from cigarette smoking (see Charania et al., 2014; and references therein). This dependence is confirmed in our study by the model subsets 1 and 2 of PC-6(All contaminants) in the multivariable analysis (see Table 5). Current non-smokers had significantly lower Cd-concentrations in whole blood compared to smokers (respectively 0.15 and 0.42 μg/L; $P_{MW} < 0.001$). These concentrations are below the level of concern of 1.12 μg/L (see Charania et al., 2014). Grains and cereals are recognized sources of Cd (e.g., Adams et al., 2011), as suggested in the model subsets mentioned.

Contaminated soil and vegetables grown in them, and drinking water remain sources of Pb for the general population; the latter source is due to Pb-plumbing in older homes (Nieboer et al., 2013). Generally speaking, smoking constitutes a minor source of Pb and this is also suggested by our data for current smokers ($P_{MW} = 0.004$). Gun use (fumes given off during gun firing contain Pb) and consumption of hunted game such as waterfowl (tissue - embedded Pb pellets and/or fragments) are also recognized as sources (Nieboer et al., 2013). The reindeer/moose/grouse predictor in model subset 2 of PC-6(All contaminants) suggests that this exposure source does indeed contribute to Pb exposure in our study group.

Magnitude of the observed element concentrations in whole blood

The current study confirms our conclusion stated in the preliminary report (Hansen et al., 2011), namely: "Generally speaking, the concentrations of the toxic elements observed in our study were relatively low. Consequently they are not of clinical importance, and thus of no special concern for pregnant women, the unborn, females of reproductive age and children" (but see comments on Pb and Cd below). This assessment also applies to Cu, Mn, Se, Zn and Mo in whole blood.

Limitations

The study group was smaller than targeted although several attempts were made through media, posters and ongoing encouragement by health professionals and field workers associated with our study. Compared to our preliminary MISA reports, the restraint on the internal and external validity was mitigated by the increased sample in the current study. Relative to our first report on OCs (Hansen et al., 2010), the current sample size increased from 50 to 266 for the 'All contaminants' group and to 498 for the 'POPs

only'; similarly for the elements, *n* increased from 219 (Hansen et al., 2011) to 266 and 279, respectively for the 'All contaminants' and 'Elements only' groups.

Since the MISA study involved only pregnant women, the matter of inhomogeneity likely pertained to the reported dietary intakes, personal & social characteristics and the measured contaminant concentrations. Our FFQ was adopted from that used in the Norwegian Women and Cancer Study (NOWAC). Only minor adjustments pertaining to fish intake were made. The NOWAC FFQ has been validated (Hjartåker et al., 2007), although not specifically for pregnant women. Generally speaking, the consumption data obtained do align with other studies (Veyhe et al., 2012). Based on the comparison for deliveries registered in the Medical Birth Registry of Norway (MBRN) for the Northern Norway counties (live born, gestational age 30 – 42, $n = 15{,}571$ for 2004 – 2006), we observed that on average the women in the MISA cohort were 1– 2 years older and smoked less while other parameters such as parity, gestational age, birth weight and Apgar score at 5 min were of comparable magnitude. On this basis we believe that our cohort is representative and bias is limited.

The elements were measures in two rounds because of workload restraints. Although there were some differences in means of some elements (Cu, Zn and Mo), the relative concentration patterns remained unaltered.

Concluding remarks

The use of PCA to generate new contaminant and dietary variables not only enhanced our understanding of the interrelationships within contaminant groups and among dietary items, but also in the identification of predictors of the measured serum/whole blood contaminant concentrations in multivariable linear regression analyses. Clearly, the linear combinations of variables generated by PCA facilitated our ability to identify prominent dietary sources of OC groups and of the prominent toxic metals Cd, Pb and Hg, as well as highlighting the importance of maternal characteristics, including pregnancy histories and smoking habits.

Although the maternal concentrations of the toxic contaminants measured were relatively low, more substantial exposures would be a concern. This is especially a worry in case of Cd for mothers who smoke cigarettes during pregnancy.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijheh.2014.12.001.

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Table S1. Study Group Characteristics

		Mean (SD[a]) or *%*	Median	Min-Max
Maternal age (years) at delivery (n=515)		30.6 (5.0)	31.0	18 - 43
Age groups:				
	<25	*13.4%*		
	25-29	*26.6%*		
	30-34	*37.5%*		
	35-39	*19.0%*		
	≥40	*3.5%*		
Income (>600 000 NOK) (n=479)		*60.1%*		
Civil status; married/cohabited (n= 515)		*95.5%*		
Education (years of school) (n=495)		15.6 (2.9)	16.0	3-24
Educational years in groups				
	<13	*18.1%*		
	13-16	*40.0%*		
	>16	*40.4%*		
Ethnic affiliation (n=515):				
	Norwegian)	*88.9%*		
	Sami	*8.2%*		
	Foreign[b]	*2.9%*		
Municipality (n=515):				
	Finnmark	*16.7%*		
	Troms	*55.3%*		
	Nordland	*28.0%*		
pp-BMI[c] (kg/m^2) (n=489)		24.4 (4.5)	23.3	17.1 - 44.1
pp-BMI[c] groups:				
	<18.5	*1.2%*		
	18.5-24.9	*64.0%*		
	25.5-29.9	*24.3%*		
	≥30.0	*10.4%*		
Smoking habits (Yes):				
	Primo pregnancy (n=500)	*18.4%*		
	Gestational week 18.2 (n=500)	*8.0%*		
	Ultimo pregnancy (n= 412)	*8.3%*		
Alcohol intake (Yes):				
	Teetotaller (n=504)	*8.3%*		
	wine before pregnancy (n=459)	*70.1%*		
	beer before pregnancy (n=452)	*53.0%*		
	wine during pregnancy (n=449)	*4.1%*		
	beer during pregnancy (n=445)	*1.6%*		

Dietary supplements during pregnancy (Yes):			
Multivitamins (n=515)	*47.8%*		
Folic acid (n=515)	*71.3%*		
Fish oil winter (≥1/week) (n=375)	*90.1%*		
Fish oil rest of year (≥1/week) (n=361)	*74.8%*		
Parity (n=504)	0.9 (0.9)	1.0	0 - 4
Previous deliveries:			
0	*40.9%*		
1	*35.3%*		
2	*18.3%*		
3	*4.8%*		
4	*0.8%*		
Sex (girl) (n=495)	*50.1%*		
Gestational age (weeks) (singletons) (n=495)	39.6 (1.5)	40.0	30-42
<37 weeks (singletons)	*3.4%*		
Birth weight in grams:			
(singletons)	3620 (514)	3580	1330-5170
<2500 g (singletons)	*1.8%*		
>4500 g (singletons)	*4.9%*		
Apgar (singletons) (n=494):			
Apgar 1 min	8.6 (1.5)	9.0	0-10
Apgar 5 min	9.5 (1.2)	10	0-10
Apgar <7 min	*1.6%*		
Lactation information (Yes) (n=232):			
Ever breastfeeding	*95.6%*		
Never exclusively breastfeeding	*4.3%*		
Never breastfeeding	*1.7%*		

[a]SD=Standard deviation. [b]Foreign: Nordic n = 6, European n = 8, Outside Europe n = 1.
[c]Pre-pergnancy BMI, based on self-reported height and pre-pregnancy weight.

Table S2. Reported daily intake of energy, macro and micronutrients for pregnant women from Northern Norway (n = 496)[a]

	Unit	Mean (SD[d])	Median or % of Total Energy	Min-Max
MJ[b,c]		8.0 (2.1)	*8.0*	2.2 – 16.4
Protein	g	81.1 (21.0)	17.3%	22.3 – 155.6
Carbohydrates	g	216.8 (59.1)	46.1%	63.8 – 460.6
Fat	g	74.1 (23.0)	34.1%	19.0 – 192.8
Saturated fat	g	29.9 (9.9)	14.0%	7.4 – 77.8
Mono-unsaturated fat	g	23.0 (7.1)	10.8%	5.7 – 55.4
Poly-unsaturated fat	g	14.0 (5.4)	6.6%	3-0 – 42.3
Sugar	g	28.1 (16.7)	5.9%	2.9 – 121.2
Fiber	g	24.2 (7.1)	2.4%	4.4 – 54.2
Retinol	µg	800.9 (379.1)	*704.2*	150.2 - 2189
β-carotene	µg	3227 (2115)	*2744*	302.0 – 12380
Vitamin-D	µg	5.4 (2.5)	*5.1*	0.5 - 17.4
Tocopherol	mg	8.1 (2.4)	*8.0*	2.1 – 17.6
Thiamine	mg	1.3 (0.3)	*1.3*	0.3 – 2.6
Riboflavin	mg	1.5 (0.4)	*1.5*	0.4 – 3.3
Niacin	mg	16.5 (4.3)	*16.4*	4.4 – 30.9
Vitamin-B6	mg	1.4 (.04)	*1.4*	0.3 – 2.5
Folate	µg	212.3 (65.0)	*206.3*	42.7 – 478.8
Vitamin-B12	µg	6.2 (2.4)	*6.1*	1.1 – 16.8
Vitamin-C	mg	114.0 (58.8)	*102.9*	11.9 – 385.0
Calcium	mg	760.6 (279.0)	*739.5*	225.0 – 1692
Iron	mg	9.8 (2.6)	*9.8*	2.3 – 18.6
Sodium	mg	2912 (786.5)	*2901*	751.5 – 5893
Potassium	mg	3440 (963.4)	*3414*	734.4 – 6597
Magnesium	mg	338.7 (89.2)	*337.0*	69.1 – 651.8
Zinc	mg	10.2 (2.8)	*10.0*	2.7 – 21.5
Selenium	µg	61.5 (18.9)	*59.5*	16.2 – 137.1
Copper	mg	1.1 (0.3)	*1.1*	0.2 – 2.4
Phosphorus	mg	1485 (394.3)	*1470*	384.1 – 2817

[a]Seven women did not hand in the FFQ and another 12 failed to fill-in all parts of FFQ. [b]Mega Joule. [c]Summation of total energy intake (MJ) was based on the intake of protein, fat, carbohydrates and fiber. [d]SD = standard deviation.

Table S3. Limits of detection (LOD) (pg g^{-1}) for POPs with detection frequencies ≥ 50% in maternal serum

Compound[a,b]	*n*[c]	LOD[d] (pg/g)	% > LOD
PCB 99	507	6	95
PCB 118	508	10	97
PCB 138	508	13	100
PCB 163	501	12	81
PCB 153	508	14	100
PCB 156	499	12	58
PCB 170	508	11	98
PCB 180	508	15	100
PCB 183	494	8	62
PCB 187	502	9	96
p,p′-DDE	508	20	100
HCB	507	30	97
trans-Nonachlor	508	1	99
cis-Nonachlor	507	1	96

[a]See Table 1 Footnote 'a' for full names. [b]Some compounds were non-detectable, difficult to quantify, or had detection frequencies ≤ 50% (PCB 101, 30%; PCB 194, 41%). [c]The variation in number of participants reflects the restrictions given in footnote 'b' of Table 1. [d]LOD = limit of detection.

Table S4. Limits of detection and detection frequencies above LOD for the elements: As, Cd, Co, Hg, Pb, Cu, Mn, Mo, Se, and Zn in maternal whole blood.

Compound[a]	Unit Wt L^{-1}	LOD[b]	n[c]	% detected > LOD
As	µg	0.19	282	98.9
Cd	µg	0.02	282	100
Co	mg	0.03	282	98.2
Hg	µg	0.15	282	99.3
Pb	µg	0.26	280	100
Cu	µg	0.002	282	100
Mn	µg	0.11	282	100
Mo	µg	0.21	282	100
Se	µg	0.93	281	100
Zn	mg	0.01	282	100

[a]See Table 2 Footnote 'a' for full names. [b]Limit of detection. [c]The variation in number of participants is due to due to the exclusion of extreme values.

Table S5. Univariable linear regression analyses for factors PC-1 to PC-6 (All contaminants) and PC-1 and PC-2 (POPs only). Predictors: maternal age, parity (0-4), breastfeeding (Yes/No), years of schooling, pp-BMI, and present smoking (when filling in FFQ: mean gestational age 18.2 weeks (Yes/No)) were all analysed as single variables. And factors PC-1 to PC-7 (Diet). Predictors: maternal age, years of school, present smoking (when filling in FFQ: mean gestational age 18.2 weeks (Yes/No), pp-BMI, physical activity before pregnancy (scale 1-10). Only results $p \leq 0.05$ are presented.

	B	95% CI	p-value	Standardized- β	R^2
PC-1 (All contaminants)					
Maternal age (n=266)	0.08	0.06 ; 0.11	<0.001	0.40	0.16
Parity (n=266)	-0.19	-0.31 ; -0.06	0.003	-0.18	0.03
Breastfeeding (n=244)	-0.39	-0.65 : -0.14	0.003	-0.19	0.04
Years at school (n=259)	0.10	0.06 ; 0.15	<0.001	0.29	0.08
Present smoking (Yes/No) (n=259)	-0.51	-1.02 ; -0.01	0.05	-0.13	0.02
PC-1 (POPs only)					
Maternal age (n=498)	0.06	0.04 ; 0.08	<0.001	0.31	0.10
Parity (n=498)	-0.11	-0.21 ; -0.02	0.02	-0.10	0.01
Breastfeeding (n=431)	-0.25	-0.41 ; -0.08	0.004	-0.14	0.02
Years at school (n=481)	0.07	0.04 ; 0.10	<0.001	0.20	0.04
pp-BMI (n=475)	-0.04	-0.06 ; -0.02	<0.001	-0.17	0.03
PC-2 (POPs only)					
Maternal age (n=498)	0.03	0.02 ; 0.05	<0.001	0.17	0.03
Parity (n=498)	-0.17	-0.26 ; -0.07	<0.001	-0.16	0.02
Breastfeeding (n=431)	-0.37	-0.56 ; -0.18	<0.001	-0.18	0.03
Years at school (n=481)	0.06	0.03 ; 0.09	<0.001	0.17	0.03
pp-BMI (n=475)	0.02	0.003 ; 0.04	0.03	0.10	0.01
PC-2 (All contaminants)					
Maternal age (n=266)	0.04	0.02 ; 0.07	0.001	0.20	0.04
Years at school (n=259)	0.05	0.01 ; 0.1	0.02	0.15	0.02
PC-3 (All contaminants)					
Parity (n=266)	0.14	0.02 ; 0.27	0.03	0.13	0.02
Breastfeeding (n=244)	0.36	0.11 ; 0.61	0.005	0.18	0.03
PC-4 (All contaminants)					
pp-BMI (n=258)	0.06	0.04 ; 0.09	<0.001	0.28	0.08

PC-5 (All contaminants)					
pp-BMI (n=258)	0.03	0.000 ; 0.05	0.05	0.12	0.02
PC-6 (All contaminants)					
Parity (n=266)	0.13	0.002 ; 0.26	0.05	0.12	0.02
Years at school (n=259)	-0.08	-0.12 ; -0.03	0.001	-0.20	0.04
Present smoking (Yes/No) (n=259)	2.50	2.09 ; 2.91	<0.001	0.60	0.36
PC-1 (Fruit & Vegetables) Diet					
Maternal age (n=496)	0.03	0.01 ; 0.05	0.001	0.14	0.02
Years at school (n=486)	0.05	0.02 ; 0.08	<0.001	0.16	0.03
Present smoking (Yes/No) (n=490)	-0.36	-0.69 ; -0.03	0.04	-0.10	0.009
pp-BMI (n=479)	-0.03	-0.04 ; -0.005	0.02	-0.11	0.01
Physical activity before pregnancy (n=492)	0.09	0.04 ; 0.15	<0.001	0.16	0.03
PC-2 (Marine fish) Diet					
Maternal age (n=496)	0.03	0.02 ; 0.05	<0.001	0.17	0.03
Physical activity before pregnancy (n=492)	0.07	0.02 ; 0.12	0.008	0.12	0.01
PC-3 (Junk food) Diet					
Maternal age (n=496)	-0.04	-0.05 ; -0.02	<0.001	-0.17	0.03
Years at school n=486)	-0.06	-0.10 ; -0.04	<0.001	-0.19	0.04
PC-4 (Grains & Dairy) Diet					
Maternal age (n=496)	0.03	0.009 ; 0.05	0.003	0.13	0.02
Years at school (n=486)	0.04	0.009 ; 0.07	0.01	0.11	0.01
PC-5 (Local traditional food) Diet					
Years at school (n=486)	0.04	0.002 ; 0.06	0.04	0.09	0.009
PC-6 (Sauce & Meat) Diet					
Years at school (n=486)	0.03	0.000 ; 0.06	0.05	0.09	0.008
PC-7 (Whale/seal & fish liver) Diet					
pp-BMI (n=479)	0.03	0.01 ; 0.05	0.001	0.15	0.02
PC-8 (Seagull eggs) Diet					
Present smoking (Yes/No) (n=490)	0.43	0.10 ; 0.77	0.01	0.11	0.01
Physical activity before pregnancy (n=491)	-0.06	-0.11 ; -0.01	0.02	-0.11	0.02