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Persistent organic pollutants in Greenlandic pregnant women and indices of foetal growth: The ACCEPT study

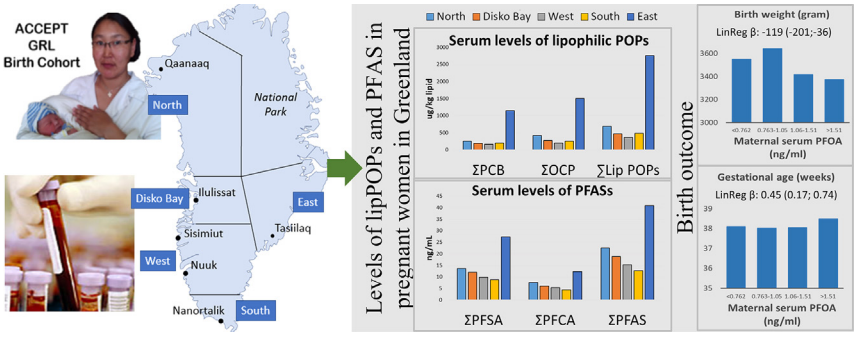
Marie Harthøj Hjermitslev [a], Manhai Long [a], Maria Wielsøe [a], Eva C. Bonefeld-Jørgensen [a,b,*]

[a] Center for Arctic Health and Molecular Epidemiology, Department of Public Health, Aarhus University, Denmark
[b] Greenland Center for Health Research, University of Greenland, Nuuk, Greenland

HIGHLIGHTS

- Significant regional differences in lifestyle factors among Greenlandic pregnant women
- Higher serum levels of lipophilic POPs and PFASs in North and East Greenland
- Inverse associations between maternal serum level of PFOA and foetal growth
- Maternal serum level of PFOA positively associated with gestational age at birth

GRAPHICAL ABSTRACT



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ABSTRACT

The Greenlandic population has some of the highest levels of environmental persistent organic pollutants (POPs) globally. Studies have previously found POPs to be linked with disturbance of child development, immune function and reproductive abilities. We investigated the associations between serum POP levels of pregnant women in Greenland and their infant's birth weight, length, head circumference and gestational age (GA) at birth.
Pregnant Greenlandic women ($n = 504$) were enrolled during pregnancy and serum levels of the lipophilic POPs (Organochlorine pesticides, Polychlorinated biphenyls and Polybrominated diphenyl ethers) and the amphiphilic POPs, Perfluoroalkylated substances (PFASs), were measured. We analysed the associations between maternal serum levels of POPs and birth weight, length, head circumference and GA using linear regression analysis. We found significant inverse associations between Perfluorooctanoic Acid (PFOA) and birth weight (adjusted $\beta = -119$ g, 95% CI: −201; −36), birth length (adjusted $\beta = -0.37$ cm, 95% CI: −0.76; 0.02, borderline significant) and head circumference (adjusted $\beta = -0.35$ cm, 95% CI: −0.59; −0.10) and a positive association with

Abbreviations: ACCEPT, Adapting to Climate Change and Environmental Pollution and Dietary Transition; AMAP, The Arctic Monitoring and Assessment Programme; BMI, body mass index; DL, detection limit; DL-PCB, dioxin-like-polychlorinated biphenyl; FFA, free fatty acids; GA, gestational age at birth; GRL, Greenland; KVUG, Ethical Committee for Scientific Investigations in Greenland; n−3/n−6, ratio of omega-3 fatty acids/omega-6 fatty acids; OCP, organochlorine pesticides; OR, odds ratio; p,p′-DDE, dichlorodiphenyltrichloroethane; p, p′-DDT, dichlorodiphenyldichloroethylene; PBB, polybrominated biphenyl; PBDE, polybrominated diphenyl ethers; PC, principal component; PCA, principal component analysis; PCB, polychlorinated biphenyl; PFASs, perfluoroalkylated substances; PFBS, perfluorobutanesulfonic acid; PFCA, perfluorinated carboxylic acid; PFDA, perfluorodecanoic acid; PFDoA, perfluorododecanoic acid; PFDS, perfuoro-1-decanesulfonate; PFHpA, perfluoroheptanoic acid; PFHpS, perfluoroheptanesulfonate; PFHxA, perfluorohexanoic acid; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PFOSA, perfluorooctane sulfonamide; PFPeA, perfluoropentanoic acid; PFSA, perfluorinated sulfonic acids; PFTeA, perfluoropentanoic acid; PFTrA, perfluorotridecanoic acid; PFUnA, perfluoroundecanoic acid; PI, Ponderal Index; POP, persistent organic pollutants; ß-HCH, β-hexachlorocyclohexane.

* Corresponding author at: Center for Arctic Health and Molecular Epidemiology, Department of Public Health, Aarhus University, 8000 Aarhus C, Denmark.
E-mail address: ebj@ph.au.dk (E.C. Bonefeld-Jørgensen).

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Birth outcome
Arctic

GA (adjusted β = 0.45 week, 95% CI: 0.17; 0.74). For the lipophilic POPs, we found an overall trend of inverse associations to foetal growth indices.
In conclusion, we found that the amphiphilic PFOA had a significant inversely association with foetal growth indices, whereas GA was positively associated. The data indicate that POPs have a negative effect on foetal growth.

1. Introduction

Persistent organic pollutants (POPs) are carbon-based chemicals originating from industrial processes and found ubiquitously in the environment. POPs are transported along sea-currents and atmospheric movement and are accumulated in the arctic areas (Barrie et al., 1992; Burkow and Kallenborn, 2000; Hung et al., 2016).

The POPs, including the lipophilic POPs (e.g. polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs) and the amphiphilic perfluoroalkylated substances (PFASs), bio-accumulate and biomagnify through the marine food chain due to their property of resistant to degradation (Borga et al., 2004; Krafft and Riess, 2015; Corsolini and Sara, 2017). The Greenlandic Inuit is therefore to a greater extent exposed to POPs since they to some degree rely on their traditional food sources from the marine food chain, such as seal, whale, walrus and polar bear (Deutch et al., 2007a; Jeppesen and Bjerregaard, 2012). Several studies have found that the body burden of lipophilic POPs in the Greenlandic Inuit is higher than that of the people living close to major emission points (Frank and Mackay, 1993; Bonefeld-Jorgensen, 2010; AMAP, 2015; Long et al., 2015). The level of POPs found in humans correlate with smoking, age and the level of n−3 polyunsaturated fatty acids (FFA), indicating that a major source of POPs in the arctic populations is marine food sources (Bonefeld-Jorgensen, 2010; Knudsen et al., 2015; Long et al., 2015).

Over the last decades, the levels of lipophilic POPs in humans have been decreasing, due to the regulation of these chemicals, leading to a reduction of POPs found in marine food sources (Abass et al., 2018). Today, the Greenlandic Inuit population in general relies less on these traditional food sources and more on imported foods and is thus less exposed to marine POP sources (Bjerregaard et al., 2013; Knudsen et al., 2015; Long et al., 2015; Terkelsen et al., 2018). Despite this development, the serum POP levels are still relatively high and of significance to report adverse effects of the POPs. Some POPs, such as the PFASs and Polybrominated diphenyl ethers (PBDEs), are not yet all listed in the Stockholm Convention, and are still used in industry and commercial products. For the PFASs, only perfluorooctane sulfonate (PFOS) are on the Stockholm Convention list, however, the Perfluorooctanoic acid (PFOA) and the Perfluorohexane sulfonate (PFHxS) are on concern and proposed for listing under the Stockholm Convention, making studies of POPs highly relevant for future regulation (Stockholm-Convention, 2009).

POPs, including PFASs, have been connected to negative effects on child cognitive development (Boucher et al., 2012; Bonefeld-Jorgensen et al., 2014; Lam et al., 2017), immune disruption (Dallaire et al., 2006; Heilmann et al., 2010; Grandjean et al., 2012; Schaebel et al., 2017), reduced reproductive ability, cancer, and metabolic defects (Bonefeld-Jorgensen et al., 2014; Ghisari et al., 2014; Weihe et al., 2016). Several studies have indicated that POPs can disrupt the endocrine system and can decrease the body's defence against oxidative stress (Bonefeld-Jorgensen et al., 2014; AMAP, 2015) and are therefore still a concern regarding the public health status in Greenland.

Previous studies have examined the relationship between prenatal exposure to POPs and foetal growth (Govarts et al., 2012; Iszatt et al., 2015) but, to our knowledge, no such study have been conducted in Greenland. Previously, we found in general Greenlandic Inuit (male and female) aged 18–73 years, that the amphiphilic PFASs to a lesser degree than the lipophilic POPs was correlated with intake of traditional marine food sources (Long et al., 2012). Importantly, it should remembered that PFAS exposures also originates from other sources including customer products e.g. impregnation spray for outdoor equipment's such as clothes and shoes, food being in close contact with packaging containing PFASs, cosmetics and indoor dust form textiles and carpeted houses along with industrial sources globally and in Greenland as well (Long et al., 2012; Wang et al., 2015).

Both the regulated lipophilic POPs and the not yet regulated amphiphilic PFASs (except PFOS) are found in humans, because of their persistence and long half-lives being between 5 and 15 years meaning the POPs we find in humans today are partly “legacy” POPs from the past (Ritter et al., 2011) as well as current exposures (Long et al., 2012; Krafft and Riess, 2015; Long et al., 2015).

The effect of POPs on humans has raised international concern and in 1991 The Arctic Monitoring and Assessment Programme (AMAP) was formed as a part of the Arctic council. Since then the AMAP project has been monitoring the contaminant levels and contributed with scientific studies that addresses the effects of environmental pollutants in the Arctic (AMAP, 2009).

In 2010, the ACCEPT birth cohort (Adapting to Climate Change, Environmental Pollution and Dietary Transition) was established as a prospective mother-child cohort in Greenland being a part of the circumpolar AMAP studies. The aim of the cohort is to determine exposure levels of contaminants, life style and diet during pregnancy, and assess possible interference with the foetal development of infant/child health. Since 2010, the ACCEPT cohort has enrolled 614 Greenlandic women and their children from different regions in Greenland (Knudsen et al., 2015; Terkelsen et al., 2018).

The aim of the present study is to determine the serum levels of POPs in the ACCEPT pregnant Greenlandic women and investigate possible associations between mother serum levels of POPs and indices of foetal growth, such as birth weight, length, head circumference and gestational age (GA).

2. Methods and materials

2.1. Study population

The present study was conducted based on a cross-sectional study. Recruitment of the pregnant women for the mother-child cohort occurred between August 2010 and August 2011 and between June 2013 and September 2015, including a total of 614 pregnant women (Knudsen et al., 2015; Terkelsen et al., 2018). Inclusion criteria was that all participants had to be ≥18 years of age, lived >50% of their lives in Greenland to be classified as Inuit and had to have at least one Inuit parent and/or have Greenlandic as their native language.

The recruitment was performed by doctors and midwifes in 16 towns from all regions in Greenland: North (Qaanaaq, Upernavik, Uummannaq), Disko Bay (Ilulissat, Aasiaat, Qeqertarsuaq, Qasigiannguit), West (Sisimiut, Maniitsoq, Nuuk, Paamiut), South (Qaqortoq, Nanortalik, Narsaq), East (Tasiilaq, Ittoqqortoormiit) (Fig. 1). Nineteen participants regretted participation or had an early abortion/miscarriages, five was under 18 years of age, 42 had lived for >50% of their lives outside of Greenland, 5 were classified as non-Inuit, 33 had missing information on life duration in Greenland and 6 participants had no blood samples, leaving a total number of 504 participants meeting the inclusion criteria. The blood samples of these 504 pregnant

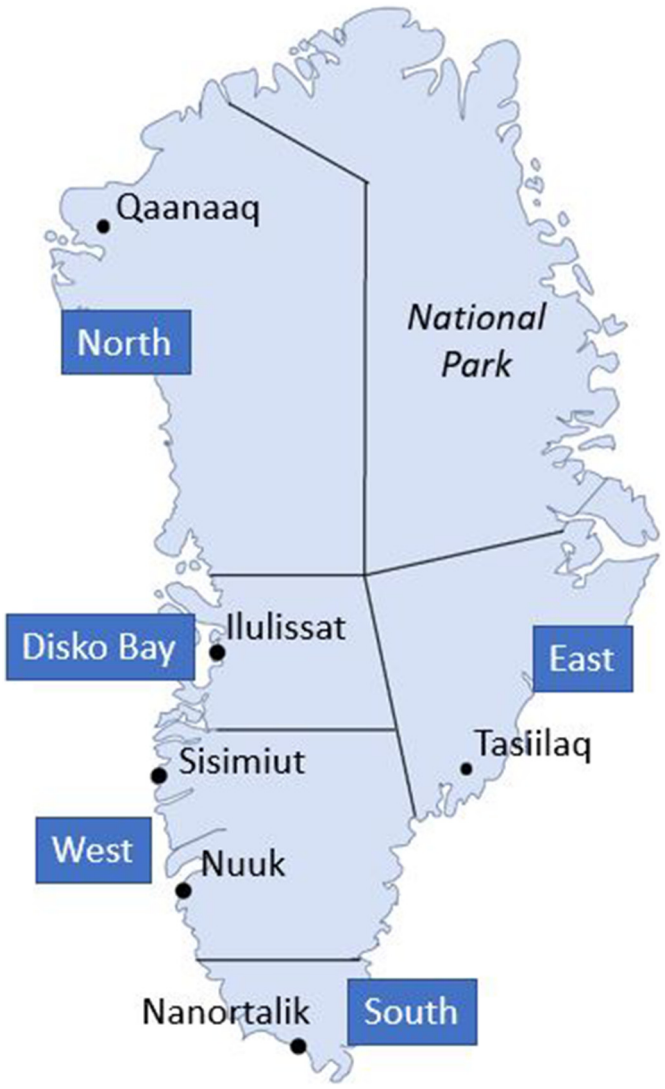

Fig. 1. Map of Greenland with the collection sites and regions.

women were collected for the evaluation of POP exposure level. During pregnancy 12 women had abortions or miscarriages, no birth outcome data was collected for five women and four twin pairs and one stillborn were excluded. This left 482 mother-child pairs available for analysis of POP exposure and birth outcomes (Fig. 2).

Informed consent was obtained from all participants prior to data collection. The women filled in lifestyle questionnaires offered in both Greenlandic and Danish. The questionnaire provided information on where the women were born and where they grew up. The women belonged to the region where they had lived longest of their life. Data on pre-pregnancy body mass index (BMI), smoking status and reproductive factors were obtained from medical records and lifestyle questionnaires (Knudsen et al., 2015; Terkelsen et al., 2018).

Venous blood samples were collected from the women at inclusion in the study. Mean gestational week of sampling in 2010–2011 was week 26.2 (range 7–40 weeks) and in 2013–2015 all samples were collected before the end of week 13. The blood samples were stored at −80 °C until analysis.

The outcome data of the new-borns were carried out by midwifes, and the research group obtained the data from the Greenlandic Doctors Office.

The study has been approved be the Ethical Committee for Scientific Investigations in Greenland (KVUG) and conducted in accordance with the Helsinki Declaration.

2.2. Serum POP contaminants

Serum blood samples were analysed for 11 OCPs, 14 PCBs and 10 PBDEs at Le Centre de Toxicologie du Québec in Canada and for 16 PFASs at the Department of Environmental Science, Aarhus University in Denmark. Details on analytical methods and specific compounds was published previously (Long et al., 2015). If samples with levels below detection limit (DL), the DL/2 were used.

2.3. Plasma cotinine levels

Cotinine is an active metabolite of nicotine and is therefore used as a biomarker to detect current tobacco smoke exposure. The cotinine concentrations were analysed using the Calbiotech Cotinine Direct ELISA Kit (Calbiotech Inc., CA, USA) at Centre of Arctic Health & Molecular Epidemiology, Aarhus University in Denmark. Levels were given in ng/ml and the detection limit was 1 ng/mL. If the values were below the detection limit the value was given as 0.5 ng/mL in the statistical analysis.

2.4. Plasma fatty acids

The ratio between n−3 polyunsaturated fatty acids (FFA) and n−6 FFA (n−3/n−6) is known to be a strong indicator of marine food intake (Deutch et al., 2004) and is used as an indicator of the consumption of Greenlandic traditional foods versus imported foods.

The analysis was made at the Biology Department, University of Guelph in Canada. Details on analytical methods and measurement methods was published previously (Long et al., 2015).

2.5. Statistical analysis

The statistical analyses of data from blood samples, lifestyle and birth outcome was performed in SPSS Statistics version 20 with a significance level of 5% ($p \leq 0.05$). Due to the sample size decrease when performing multiple regression analysis, p value ≤0.08 was considered a borderline significant.

All investigated POPs and groupings are listed in Table 1. We grouped the PFASs based on their chemical structure: ∑Perfluorinated sulfonic acids (PFSA) including 6 PFSAs and ∑Perfluorinated carboxylic acid (PFCA) including 10 PFCAs. We grouped ∑PCB including 14 PCBs and ∑OCP including 11 OCPs since we previously found high correlation within the lipophilic POP groups (Van den Berg et al., 2006; Deutch et al., 2007b; Long et al., 2015).

In line with previous studies from our group we grouped PCB 105, PCB118 and PCB 156 as ∑DL-PCB as they are dioxin-like PCBs (Van den Berg et al., 2006; Long et al., 2015).

Compounds which were above detection limit in >50% of the samples were also analysed individually.

Data was analysed as either continuous data or categorical data. The distribution of the continuous data was tested with Kolmogorov-Smirnov and Shapiro Wilk test. The natural logarithmic (ln) transformed variables made the distribution more symmetrical and thus the analysis was performed on the ln-transformed data.

Associations between exposure and birth outcome were examined using multiple linear regression analysis. We chose our core adjustments based on literature search: Mother age, pre-pregnancy BMI, parity, smoking status (represented by plasma cotinine levels) and alcohol consumption during pregnancy (Bach et al., 2016; Tang et al., 2018). We tested the assumptions of the multiple linear regression using variance inflation factors. All assumptions were met. The linear regression analysis of POP exposure and birth outcome was further stratified for child gender. We then further adjusted for GA, knowing that time of gestation being important for foetal growth.

In addition to core adjustments, we adjusted one by one for income, educational level and n−3/n−6 to explore the effect of these factors.

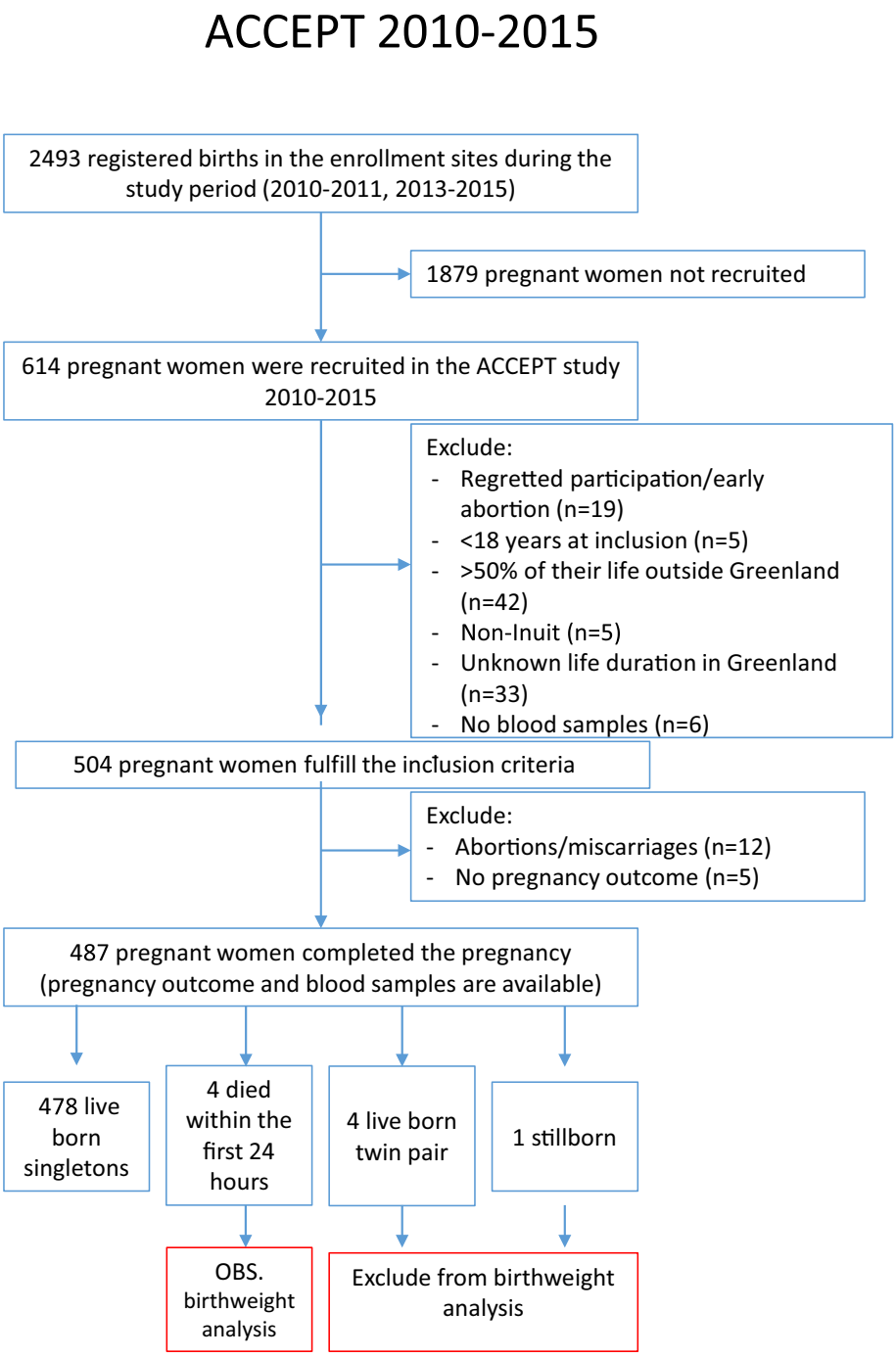

Fig. 2. Flowchart for inclusion of study participants.

We searched for associations between prenatal POP exposure and preterm birth (<37 weeks) and low birth weight (<2500 g) using logistic regression to calculate odds ratio (OR), adjusting for mother age, pre-pregnancy BMI, parity, the smoking biomarker cotinine and consumption of alcohol during pregnancy.

2.6. Principal component analysis (PCA)

The use of a large number of individual parameters would create a certain number of false positive results when performing multiple comparisons. Principal component analysis (PCA) is a powerful multivariate analytical tool and is applied to reduce a set of original variables and to extract a smaller number of principal components. Using PCA for data transformation is a common ad hoc tool to deal with multi-collinearity in multiple regression models because the correlation between related compounds such as lipophilic POPs and PFAS congeners exists and this multi-collinearity biases the estimation of individual regression coefficients to cause misleading interpretation of the effects of individual predictor variables (Los, 1989; Jolliffe and Cadima, 2016). PCA reduces the false positives by reducing the number of variables (Liberda et al., 2014). Besides, people are exposed to the mixture of different substances simultaneously, it is important to assess the effect of actual effect of mixture and PCA might provide the possibility to address this issue. Therefore, we further used PCA to identify potential underlying components of levels of lipophilic POPs (PCBs, OCPs, PBDEs) and PFASs in serum samples. By PCA the

Table 1
Group of POPs included in the analysis.

∑PCB	∑OCPs	∑LegacyPOPs	∑PBDE	∑LipophilicPOPs	∑PFSA	∑PFCA	∑PFAS
PCB 101	Aldrin	∑PCB	PBDE 100	∑PCB	PFBS	PFPeA	∑PFSA
PCB 105	alpha-Chlordane	∑OCP	PBDE 15	∑OCP	PFHxS	PFHxA	∑PFCA
PCB 118	cis-Nonachlor		PBDE 153	∑PBDE	PFHpS	PFHpA	
PCB 128	gamma-Chlordane		PBDE 17		PFOS	PFOA	
PCB 138	Hexachlorobenzene		PBDE 25		PFDS	PFNA	
PCB 153	Mirex		PBDE 28		PFOSA	PFDA	
PCB 156	Oxychlordane		PBDE 33			PFUnA	
PCB 170	p,p′-DDE		PBDE 47			PFDoA	
PCB 180	p,p′-DDT		PBDE 99			PFTrA	
PCB 183	ß-HCH		PBB 153			PFTeA	
PCB 187	trans-Nonachlor						
PCB 28							
PCB 52							
PCB 99							
∑DL-PCB							
PCB105							
PCB118							
PCB156							

PCB: polychlorinated biphenyl, DL-PCB: Dioxin-like-polychlorinated biphenyl, OCP: organochlorine pesticides, p,p′-DDE: dichlorodiphenyltrichloroethane, p,p′-DDT: dichlorodiphenyldichloroethylene, ß-HCH: β-hexachlorocyclohexane, PBDE: polybrominated diphenyl ether, PBB: polybrominated biphenyl, PFSA: Perfluoroalkylated substances, PFBS: perfluorobutanesulfonic acid, PFHxS: perfluorohexane sulfonate, PFHpS: perfluoroheptanesulfonate, PFOS: perfluorooctane sulfonate, PFDS: perfuoro-1-decanesulfonate, PFOSA: perfluorooctane sulfonamide, PFCA: perfluorinated carboxylic acid, PFPeA: perfluoropentanoic acid, PFHxA: Perfluorohexanoic acid, PFHpA: perfluoroheptanoic acid, PFOA: perfluorooctanoic acid, PFNA: perfluorononanoic acid, PFDA: perfluorodecanoic acid, PFUnA: perfluoroundecanoic acid, PFDoA: perfluorododecanoic acid, PFTrA: perfluorotridecanoic acid, PFTeA: perfluoropentanoic acid.

correlated variables are grouped together. The coefficients defining these linear combinations, termed as "factor loadings", are the correlations of each input variables with the component. The biomarkers which were detectable in >1% of all serum samples were input into the model to extract principal components (PCs). The number of PCs was extracted based on the eigenvalues >1 and Varimax rotation (Newby and Tucker, 2004). The Kaiser-Mayer-Olkin test (0.916) and Bartlett Test of Sphericity ($p < 0.001$) were used for testing the suitability of analysis. All factors loading >|0.3| were used to identify the variables comprising a PC.

3. Results

3.1. Lifestyle characteristics

Baseline characteristics of the study population are presented in Table 2. Of the included 504 pregnant Greenlandic women, 56.8% belonged to the region West. The median age was 27 years (range 18–42 years) and pre-pregnancy BMI median for the study population was 24.4 kg/m^2.

We found significant difference in self-reported smoking status in the beginning of their pregnancy across the regions ($\rho = 0.006$): 76.5% of the participants from region East were smokers, 40.6% from North, 40.9% from the South, 34.1% from West and 31.7% Disko Bay. There was a significant difference in the plasma cotinine levels between smokers and non-smokers (mean non-smokers 9.4 ng/mL vs smokers 74.8 ng/mL: median: 0.5 vs. 63.7 ng/mL, $\rho < 0.0001$). Among the regions, the alcohol consumption before pregnancy was significantly different ($\rho = 0.033$) while only borderline difference was observed for the alcohol consumption during pregnancy ($\rho = 0.086$) which might be due to the decreased sample size.

A significant difference in parity were found across regions ($\rho = 0.013$). Parity, defined as full-term pregnancy, was higher in the North and East region, where 24.1% and 18.8% respectively had ≥3 full-term pregnancies, compared to 10.2%, 10.2% and 8.8% in Disko Bay, West and South respectively. In all regions, except the North, most of the women (50–63%) had 1–2 pregnancies. The n−3/n−6 ratio was not significantly different among the regions, although a slightly higher value observed in the East region (Table 2).

3.2. Serum concentrations of POPs

The serum concentration of the summed POP groups and the individual POPs are presented in Table 3. All summed congeners were higher in the East and North region. The median serum level of ∑PCB was 1145 μg/kg lipid in East and 257.4 μg/kg lipid in North region, compared to 188, 158 and 196 μg/kg lipid in Disko Bay, West and South respectively ($\rho < 0.0001$). The same trend was seen for ∑OCP where the median serum level in the East region was 1501 μg/kg lipid and in the North region 416 μg/kg lipid compared to 273, 196 and 256 μg/kg lipid in the Disko Bay, West and South regions respectively ($\rho < 0.0001$). The summed PFAS groups had similar pattern, for ∑PFASs, the East and North regions had the highest level, with 40.8 ng/mL serum and 22.5 ng/mL serum, respectively while in Disko Bay, West and South, the ∑PFAS levels were 18.8, 15.2 and 12.7 ng/mL serum, respectively ($\rho < 0.0001$) (Table 3).

3.3. Birth outcome characteristics

We found similar birth outcome characteristics in all regions, with no significant differences (Table 4). The birth outcomes for all regions were as follows: median birth weight was 3615 g, median birth length 51 cm, median head circumference 35 cm and median GA at birth week 39. In total, including all regions, there were 28 preterm birth, with GA at birth in the range of 22–36 week. The offspring included 52.5% males.

3.4. Correlation between serum POPs and lifestyle factors

Table 5 presents data of the correlation analysis between POPs and lifestyle factors using Spearman correlation coefficient. The lipophilic POPs were all significantly and positively correlated with age, p-cotinine and n−3/n−6 ratio. All summed PFASs data (∑PFASs, ∑PFSAs, ∑PFCAs) were significantly positively associated to the n−3/n−6 ratio. However, the correlation coefficient of n−3/n−6 with lipophilic POPs and PFASs were <0.3. The sum of the sulfonated sulfonic acids (∑PFSAs) were significantly correlated with age, and the sum of carboxylated acid (∑PFCAs) borderline significantly correlated with p-cotinine. None of the POPs were correlated with BMI.

Table 2
Characteristics of the study population: Pregnant Greenlandic women in ACCEPT cohort.

	Region	North	Disko Bay	West	South	East	*p*-Value	All GRL towns
	N (%)	33 (6.55)	122 (24.2)	286 (56.8)	44 (8.73)	19 (3.77)		504 (100)
Age (years)	n	33	122	286	44	19	0.222*	504
	Mean ± SD	28.4 ± 4.25	27.1 ± 5.09	27.3 ± 5.05	28.60 ± 4.12	27.4 ± 5.56		27. 5 ± 4.96
	Median (min–max)	27.0 (20–36)	27.0(18–41)	27.0 (18–42)	29.0 (20–41)	28.0 (19–38)		27.0 (18–42)
BMI (kg/m^2)	n	31	118	268	43	16	0.403*	476
	Mean ± SD	24.3 ± 3.57	25.8 ± 5.23	25.7 ± 4.96	25.0 ± 4.82	27.0 ± 6.01		25.6 ± 4.98
	Median (min–max)	23.5(18.7–33.6)	24.7(17.6–39.4)	24.5(16.4–46.6)	24.0(17.5–39.5)	24.7(19.3–39.0)		24.4(16.4–46.6)
Smoking status	n	32	120	276	44	17	**0.006**#	489
	Yes (%)	13 (40.6)	38 (31.7)	94 (34.1)	18 (40.9)	13 (76.5)		176 (36.0)
P-Cotinine (ng/mL)								
Non-smokers	n	19	82	182	26	3	0.583*	312
	Mean ± SD	23.0 ± 77.1	9.14 ± 25.7	7.83 ± 27.3	12.5 ± 35.0	2.83 ± 4.04		9.44 ± 32.6
	Median (min–max)	0.50 (0.50–338)	0.50 (0.50–145)	0.50 (0.5–254)	0.50 (0.50–171)	0.50 (0.50–7.50)		0.50 (0.50–338)
Smokers	n	13	38	93	18	4	0.441*	166
	Mean ± SD	53.0 ± 53.6	107 ± 85.5	69.0 ± 65.7	49.9 ± 45.5	99.5 ± 66.3		75.1 ± 70.2
	Median (min–max)	46.7 (0.50–160)	101 (0.50–473)	53.2 (0.50–298)	45.2 (0.50–126)	107 (13.3–171)		64.3 (0.50–473)
All	n	32	120	274	44	7	0.156*	478
	Mean ± SD	35.2 ± 69.2	40.2 ± 69.4	28.5 ± 52.9	27.8 ± 43.3	58.1 ± 69.8		32.3 ± 58.1
	Median (min–max)	0.50 (0.50–338)	0.50 (0.50–473)	0.50 (0.50–298)	0.50 (0.5–170.5)	13.3 (0.50–171)		0.50 (0.50–473)
Alcohol consumption								
Before pregnancy	n	31	110	258	41	18	**0.033**#	458
	<1 time a month (%)	12 (38.7)	47 (42.7)	127 (49.2)	24 (58.5)	7 (38.9)		217 (47.4)
	1 time a month (%)	2 (6.5)	20 (18.2)	40 (15.5)	6 (14.6)	4 (22.2)		72 (15.7)
	2–3 times a month (%)	14 (45.2)	20 (18.2)	64 (24.8)	6 (14.6)	6 (33.3)		110 (24.0)
	>1 time a week (%)	3 (9.7)	23 (20.9)	27 (10.5)	5 (12.2)	1 (5.6)		59 (12.9)
During pregnancy	n	25	74	178	31	12	0.086#	320
	<1 time a month (%)	23 (92.0)	73 (98.6)	176 (98.9)	30 (96.8)	12 (100.0)		314 (98.1)
	1 time a month (%)	1 (4.0)	1 (1.4)	2 (1.1)	1 (3.2)	0 (0.0)		5 (1.5)
	2–3 times a month (%)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		1 (0.3)
Reproductive factors								
Parity	n	29	108	245	35	16		433
	Mean ± SD	1.03 ± 0.87	1.20 ± 1.09	0.95 ± 0.97	0.86 ± 0.91	1.81 ± 1.72	**0.013***	1.04 ± 1.04
	Median (min–max)	1.00 (0–3)	1.00 (0–6)	1.00 (0–5)	1.0 (0–3)	2.00 (0–7)		1.00 (0–7)
	0 (%)	9 (31.0)	29 (26.9)	95 (38.8)	14 (41.2)	6 (18.8)	0.108#	150 (34.7)
	1–2 (%)	13 (44.8)	68 (63.0)	125 (51.0)	17 (50.0)	10 (62.5)		233 (53.9)
	≥3 (%)	7 (24.1)	11 (10.2)	25 (10.2)	3 (8.8)	3 (18.8)		49 (11.3)
n−3/n−6 ratio	n	33	122	285	44	19	0.277*	503
	Mean ± SD	0.24 ± 0.10	0.24 ± 0.12	0.25 ± 0.13	0.23 ± 0.10	0.28 ± 0.10		0.24 ± 0.12
	Median (min–max)	0.22 (0.11–0.55)	0.21 (0.09–1.20)	0.21 (0.07–0.88)	0.22 (0.09–0.62)	0.26 (0.13–0.57)		0.21 (0.07–1.20)

N: total number of participants in the region. n: total number of participants having information for the parameter. GRL: Greenland. 15 towns are included.
* p-Value was calculated with One-way ANOVA analysis on ln-transformed data.
\# p-Value was calculated with Chi square test.

Supplementary Table S1 presents the associations between the lipophilic POPs and the PFASs. All substances were significantly and positively correlated.

3.5. Associations between birth outcome and serum level of POPs

In Tables 6, 7 and supplementary Table S2, S3, results from the analyses of the associations between prenatal POP exposure and birth outcome are presented. We found that the concentration of PFOA was significantly inversely associated with birth weight upon adjustment for core adjustments (age, cotinine, parity, alcohol consumption, pre-pregnancy BMI) and further adjusted for GA ($\beta = -119$ g, $\rho = 0.005$, Table 6). PCB 156, PCB 170, Hexachlorobenzene and PFHpS were significantly inversely associated with birth weight, however, the significance disappeared upon adjusting for confounders (Table 6). PCB180, PCB 99, Cis-Nonachlor, Mirex, and trans-Nonachlor were borderline inversely associated with birth weight in some of the models ($p = 0.058$–0.070, Table 6).

PCB99 was significantly ($p = 0.043$), PCB 105 ($p = 0.061$) and trans-nonachlor ($p = 0.071$) borderline, inversely associated with birth length after core adjustment, but the significance disappeared after further adjustment for GA (Table S2). However, the birth length and PFOA was borderline significantly inversely associated after adjustment for core adjustment and GA with $\beta = -0.37$ cm, ($\rho = 0.061$, Table S2).

The head circumference and PFOA was significantly inversely associated, $\beta = -0.35$ cm ($\rho = 0.006$), after adjustment for core adjustments and GA. PFHpS showed a borderline inverse association with head circumference ($\beta = -0.89$ cm, $\rho = 0.063$), but the significance disappeared after covariates adjustment (Table S3).

With respect to GA, significant inverse association with an array of POP exposures (sumPCB, PCB118, PCB138, PCB 153, PCB 183, PCB 99, PCB 105, sum dioxin-like PCB, Mirex, Oxychlordane and ß-HCH) after core adjustment were observed ($p = 0.027$–0.050), while for PCB 187 a borderline ($p = 0.063$) negatively association with GA was found (Table 7). Sum legacy POPs and sum lipophilic POPs were significantly inversely associated with GA age at birth (adjusted $\beta = -0.0004$, $\rho = 0.05$). In contrast, PFOA was positively associated with GA at birth ($\beta = 0.45$, $\rho = 0.002$) upon core adjustments (Table 7).

We stratified by child gender and found for the female children adjusted data, that PFOA was inversely associated with birth weight ($\beta = -161$ g, $\rho = 0.010$, Table S4) and head circumference ($\beta = -0.51$ cm, $\rho = 0.006$, Table S6).

Table 3
Exposure levels of specific POPs in study population in geographical districts: Greenlandic pregnant women in ACCEPT cohort.

	% over DL		North	Disko Bay	West	South	East	p-Value*	All
PCBs (ug/kg lipid)		n	33	117	280	42	19		491
∑PCB		Median (min–max)	257 (57.1–2714)	188 (56.5–594)	158 (37.0–2391)	196 (64.1–469)	1145 (149–6731)	<**0.0001**	178 (37.0–6731)
PCB118	98.6%	Median (min–max)	14.0 (2.40–63.0)	11.1 (2.20–38.0)	7.30 (0.50–74.0)	7.50 (1.80–40.0)	23.0 (1.00–260)	<**0.0001**	8.40 (0.50–260)
PCB138	100%	Median (min–max)	39.0 (4.80–180)	28.0 (4.30–110)	23.0 (2.40–410)	33.5 (6.20–82.0)	190 (20.0–1300)	<**0.0001**	26.0 (2.40–1300)
PCB153	100%	Median (min–max)	86.0 (8.90–950)	59.5 (8.40–210)	47.0 (5.10–910)	63.0 (12.0–180)	405 (43.0–2700)	<**0.0001**	53.0 (5.10–2700)
PCB156	80.4%	Median (min–max)	4.40 (0.50–75.0)	3.00 (0.50–13.0)	3.00 (0.50–27.0)	3.10 (0.50–11.0)	10.5 (1.40–54.0)	<**0.0001**	3.10 (0.50–75.0)
PCB170	99.0%	Median (min–max)	14.0 (2.00–390)	8.60 (1.00–35.0)	7.90 (1.30–130)	11.0 (2.50–27.0)	65.5 (7.90–330)	<**0.0001**	9.10 (1.0–390)
PCB180	100%	Median (min–max)	37.0 (6.60–810)	25.0 (3.90–110)	23.0 (3.80–370)	32.5 (7.30–82.0)	170 (23.0–1100)	<**0.0001**	26.5 (3.80–1100)
PCB 183	82.1%	Median (min–max)	4.90 (0.50–20.0)	3.20 (0.50–12.0)	2.70 (0.50–75.0)	4.10 (0.50–11.0)	24.5 (2.50–200)	<**0.0001**	3.20 (0.50–200)
PCB187	98.3%	Median (min–max)	19.0 (3.40–100)	12.0 (1.00–45.0)	11.0 (1.00–230.0)	15.0 (2.90–35.0)	80.5 (8.40–610)	<**0.0001**	13.0 (1.00–610)
PCB 99	72.5%	Median (min–max)	10.0 (2.00–37.0)	9.50 (2.00–37.0)	6.00 (1.50–120)	8.00 (2.00–23.0)	56.5 (2.00–350)	<**0.0001**	8.00 (1.50–350)
PCB105	44.4%	Median (min–max)	3.00 (0.50–13.0)	2.00 (0.40–6.70)	1.00 (0.50–15.0)	1.00 (0.50–4.40)	9.30 (0.50–38.0)	<**0.0001**	1.60 (0.40–38.0)
∑DL-PCB		Median (min–max)	20.1 (3.40–139)	16.3 (3.80–54.0)	12.1 (1.50–105)	13.9 (3.9–33.1)	69.1 (10.9–345)	<**0.0001**	14.0 (1.50–345)
OCPs (ug/kg lipid)		n	33	117	280	42	19		491
∑OCP		Median (min–max)	416 (41.1–1762)	273 (52.7–953)	196 (17.6–3585)	256 (50.6–632)	1501 (122–11,863)	<**0.0001**	233 (17.6–11,863)
cis-Nonachlor	94.4%	Median (min–max)	15.0 (1.90–61.0)	10.0 (1.40–43.0)	6.90 (0.45–100)	8.65 (0.83–21.0)	38.0 (1.90–200)	<**0.0001**	8.45 (0.45–200)
Hexachlorobenzene	99.7%	Median (min–max)	40.0 (5.80–130)	32.0 (9.60–100)	23.0 (2.50–170)	26.0 (8.90–56.0)	66.0 (16.0–240)	<**0.0001**	26.0 (2.5–240)
Mirex	70.6%	Median (min–max)	4.10 (1.00–54.0)	2.75 (0.50–12.0)	2.30(0.45–47.0)	3.75 (0.50–11.0)	17.5 (0.50–120)	<**0.0001**	2.70 (0.45–120)
Oxychlordane	98.3%	Median (min–max)	40.0 (2.00–470)	23.0 (2.60–110)	15.0 (0.30–260.0)	21.5 (1.00–55.0)	130 (3.80–920)	<**0.0001**	17.0 (0.30–920)
p,p′ DDE	99.3%	Median (min–max)	230 (18.0–990)	145 (22.0–540)	110 (5.00–2500)	140 (26.0–430)	990 (83.0–8800)	<**0.0001**	120 (5.00–8800)
ß_HCH	91.0%	Median (min–max)	5.00 (0.50–34.0)	4.40 (0.50–18.0)	3.10 (0.50–28.0)	3.90 (0.50–9.20)	12.5 (3.50–64.0)	<**0.0001**	3.60 (0.50–64.0)
trans_Nonachlor	98.1%	Median (min–max)	77.0 (7.60–320)	52.5 (7.60–220)	35.0 (1.00–580)	45.5 (3.20–110)	220 (8.10–1600)	<**0.0001**	42.0 (1.00–1600.0)
∑Legacy POPs		Median (min–max)	674 (98.2–4323)	455 (85.4–1547)	351 (55.3–5976)	470 (120–1066)	2740 (271–18,594)	<**0.0001**	416 (55.3–18,594)
∑Lipophilic POPs		Median (min–max)	683 (106–4333)	464 (132–1553)	361 (61.8–5988)	480 (129–1075)	2752 (279–18,614)	<**0.0001**	424 (61.8–18,614)
PFSAs (ng/mL)		n	32	122	283	43	19		499
∑PFSA		Median (min–max)	13.6 (3.01–56.9)	12.0 (3.35–47.9)	9.83 (2.40–65.7)	8.67 (4.43–20.19)	27.2 (5.25–47.7)	<**0.0001**	10.5 (2.40–65.7)
PFOS	100%	Median (min–max)	11.9 (2.00–50.7)	10.5 (2.40–43.6)	8.40 (1.50–61.3)	7.30 (3.20–18.0)	24.2 (4.20–42.5)	<**0.0001**	8.99 (1.50–61.3)
PFHxS	99.8%	Median (min–max)	0.63 (0.10–4.48)	0.49 (0.13–2.52)	0.50 (0.04–2.57)	0.38 (0.17–1.37)	1.82 (0.20–4.34)	<**0.0001**	0.51 (0.04–4.48)
PFHpS	74.7%	Median (min–max)	0.23 (0.06–1.44)	0.19 (0.06–0.96)	0.15 (0.06–1.15)	0.13 (0.06–0.34)	0.46 (0.06–0.92)	<**0.0001**	0.16 (0.06–1.44)
PFCAs (ng/mL)		n	32	122	283	43	19		499
∑PFCA		Median (min–max)	7.47 (1.87–19.2)	6.02 (2.24–30.4)	5.32 (1.43–32.8)	4.42 (2.33–16.0)	12.3 (3.21–27.58)	<**0.0001**	5.60 (1.43–32.8)
PFOA	99.8%	Median (min–max)	1.14 (0.23–2.27)	1.09 (0.24–7.26)	1.06 (0.10–6.33)	0.85 (0.30–2.42)	1.36 (0.33–3.24)	0.300	1.06 (0.10–7.26)
PFNA	100%	Median (min–max)	1.37 (0.34–7.34)	1.25 (0.39–7.87)	1.08 (0.21–7.71)	0.90 (0.43–3.35)	3.19 (0.75–5.93)	<**0.0001**	1.15 (0.21–7.87)
PFDA	99.9%	Median (min–max)	1.01 (0.22–3.30)	0.86 (0.21–3.92)	0.66 (0.12–7.84)	0.57 (0.19–1.62)	1.55 (0.39–4.35)	<**0.0001**	0.71 (0.12–7.84)
PFUnA	99.3%	Median (min–max)	2.31 (0.28–12.1)	1.78 (0.21–16.3)	1.22 (0.08–14.9)	0.99 (0.16–5.36)	3.87 (0.42–18.2)	<**0.0001**	1.42 (0.08–18.2)
∑PFAS		Median (min–max)	22.5 (4.87–75.2)	18.8 (5.59–78.3)	15.2 (3.83–96.4)	12.7 (6.76–30.5)	40.8 (10.04–67.96)	<**0.0001**	16.2 (3.83–96.4)

n = Number of participants having information for the parameter.
DL: detection limits.
* p-Value was calculated with One-way ANOVA analysis on ln-transformed data.

Table 4
Birth outcome characteristics of Greenlandic newborns in ACCEPT cohort.

	Region	North	Disko Bay	West	South	East	*p*-Value*	All regions
Birth weight (gram)	n	31	115	274	44	18		482
	Mean ± SD	3357 ± 614	3602 ± 614	3594 ± 581	3615 ± 490.7	3425 ± 330		3575 ± 571
	Median	3455	3640	3615	3573	3350	0.322	3615
	Min–Max	1383–4330	2064–5315	585–5170	2642–4850	2775–3975		585–5315
Birth length (cm)	n	31	115	274	44	18		482
	Mean ± SD	50.3 ± 2.6	51.4 ± 2.53	51.4 ± 3.15	51.4 ± 2.4	50.6 ± 1.85	0.471	51.3 ± 2.88
	Median	50.0	51.0	51.0	51.0	50.0		51.0
	Min–Max	(41.0–54.0)	(43.0–58.0)	(24.0–58.0)	(46.0–57.0)	(48.0–54.0)		(24.0–58.0)
Head circumference (cm)	n	31	113	274	44	18		480
	Mean ± SD	33.8 ± 1.9	34.7 ± 1.56	34.7 ± 1.84	34.6 ± 1.3	34.1 ± 0.70	0.073	34.6 ± 1.72
	Median	34.0	35.0	35.0	34.7	34.0		35.0
	Min–Max	31.0–37.0	30.0–38.5	20.5–38.5	32.0–37.0	33.0–35.0		20.5–38.5
Gestational week at birth	n	30	112	266	43	14	0.423	465
	Mean ± SD	38.5 ± 2.1	39.0 ± 1.53	39.2 ± 2.07	39.3 ± 1.4	38.6 ± 1.51		39.1 ± 1.89
	Median	39.0	39.0	39.5	39.0	38.5		39.0
	Min–Max	32.0–41.0	33.0–42.0	22.0–42.0	36.0–42.0	36.0–41.0		22.0–42.0
Preterm birth <37 week	n	4	8	14	1	1	0.833	28
	Mean ± SD	34.5 ± 1.9	35.4 ± 0.92	33.7 ± 4.46	36.0 ± 0.0	36.0 ± 0.0		34.5 ± 3.31
	Median (min–max)	35.0	36.0	36.0	36.0	36.0		36.0
	Min–Max	32.0–36.0	34.0–36.0	22.0–36.0	36.0–36.0	36.0–36.0		22.0–36.0
Gender								
Male	n(%)	18(58.1)	50(43.5)	150(54.7)	27(61.4)	8(44.4)	0.097#	253(52.5)
Female	n(%)	13(41.9)	65(56.5)	124(45.3)	16(36.4)	10(55.6)		228(47.3)
Missing	n(%)	0	0	0	1(2.3)	0		1(0.2)

* p-Value was calculated with One-way ANOVA analysis on ln-transformed data.
\# p-Value was calculated with chi-Square test.

We found positive significant associations between GA and PFOA both for the male children (adjusted $\beta = 0.42$, $\rho = 0.043$) and female children (adjusted $\beta = 0.48$, $\rho = 0.019$) (Table S7). For female children we found significant inverse associations between GA and PCB153 (adjusted $\beta = -0.003$, $\rho = 0.047$), PCB 105 (adjusted $\beta = -0.09$, $\rho = 0.049$), Oxychlordane (adjusted $\beta = -0.006$, $\rho = 0.033$), ß-HCH (adjusted $\beta = -0.06$, $\rho = 0.025$) and PFHxS (adjusted $\beta = -0.57$, $\rho = 0.019$) (Table S7).

We stratified for birth week, only analysing the data for the children born to term (GA 37–42 weeks) to evaluate if term birth had influence on our results presented in Table S8-S10. Inversely significant associations between mother serum levels of some PCB congeners and OCP congeners and birth weight and birth length were observed both before and after core adjustment (Table S8 & S9). PFHxS, PFHpS, PFOS, PFOA and PFNA inversely associated with birth weight in raw data while upon core adjustment only PFHpS persisted the inversely significant association to birth weight and PFOA upon further adjustment for GA (Table S8). No significant associations between PFASs and birth length were observed both before and after adjustment but PFOA borderline (Table S9). All PFASs (except for PFUnA) were significantly inverse associated with head circumference in the raw analyses, and the significance persisted for PFHpS, PFOA and PFNA after core adjustment, and PFOA and PFNA also upon further adjustment for GA, significantly and borderline, respectively (Table S10).

We used logistic regression analysis to evaluate the associations between POPs exposure and preterm birth (birth <37 week) and observed PFOA significantly inversely associated to preterm birth (OR = −0.146, $p = 0.011$). No significant associations between low birth weight (<2500 g) and POPs were found (Data not shown).

We evaluated the impact of income, educational level and n−3/n−6 ratio, one factor at a time. But no significant changes of associations were found, and data is therefore not shown here.

3.6. Principal component analysis (PCA) results (searching for principle components of POPs and associations with birth outcomes)

When 13 PCBs, 9 OCPs, 5 PBDEs and 10 PFAS congeners were used as input variables in PCA, six distinct principal components were identified (Table S11 and S12). The first principal component (PC-1) mainly had high factors loading for most PCB and OCP congeners and explained 47.93% of the total variation in the original POP concentrations. The second identified principal component (PC-2) had a high factor loading for most PFASs and explained 14.58% of the total variation in the original POP concentrations. The third identified principal component (PC-3)

Table 5
Spearman correlation coefficient (r_s) between the sums of POPs and lifestyle factors.

	Age (years)			BMI (kg/m^2)			Plasma cotinine (ng/mL)			n−3/n−6		
	n	r_s	p	n	r_s	p	n	r_s	p	n	r_s	p
∑PCB (μg/kg lipid)	**491**	**0.14**	**0.002**	463	−0.07	0.135	**478**	**0.18**	<**0.0001**	**490**	**0.21**	<**0.0001**
∑DL-PCB (μg/kg lipid)	**491**	**0.19**	<**0.0001**	463	−0.01	0.870	**478**	**0.13**	**0.001**	**490**	**0.29**	<**0.0001**
∑OCP (μg/kg lipid)	**491**	**0.12**	**0.007**	463	−0.03	0.564	**478**	**0.20**	<**0.0001**	**490**	**0.25**	<**0.0001**
∑LegacyPOPs (μg/kg lipid)	**491**	**0.13**	**0.004**	463	−0.05	0.326	**478**	**0.20**	<**0.0001**	**490**	**0.24**	<**0.0001**
∑LipPOP (μg/kg lipid)	**491**	**0.13**	**0.004**	463	−0.05	0.302	**478**	**0.20**	**0.022**	**490**	**0.24**	<**0.0001**
∑PFSA (ng/mL)	**499**	**0.10**	**0.033**	471	−0.03	0.591	486	0.02	0.626	**498**	**0.30**	<**0.0001**
∑PFCA (ng/mL)	499	0.02	0.740	471	−0.07	0.138	486	0.09	0.052*	**498**	**0.31**	<**0.0001**
∑PFAS (ng/mL)	499	0.07	0.129	471	−0.04	0.394	486	0.05	0.255	**498**	**0.32**	<**0.0001**

Significant correlations are marked in bold (p-value <0.05).
* Borderline significant p-value ≤0.08.

Table 6
Linear regression analysis of the associations between serum level of POPs and birth weight (gram).

	Unadjusted data			Adjusted[a]			Adjusted[b]		
	n	β (95% CI)	p-Value	n	β (95% CI)	p-Value	n	β (95% CI)	p-Value
PCB (ug/kg lipid)									
∑PCB	470	−0.08 (−0.18, 0.02)	0.127	258	−0.20 (−0.49, 0.09)	0.180	248	0.003 (−0.23, 0.24)	0.978
PCB 118	470	−1.82 (−4.52, 0.88)	0.185	258	−5.13 (−10.9, 0.64)	0.081	248	−1.50 (−6.26, 3.26)	0.534
PCB 138	470	−0.34 (−0.87, 0.20)	0.217	258	−1.54 (−3.43, 0.35)	0.110	248	−0.26 (−1.82, 1.30)	0.742
PCB 153	470	−0.19 (−0.44, 0.07)	0.144	258	−0.57 (−1.36, 0.226)	0.159	248	−0.002 (−0.65, 0.65)	0.995
PCB 156	**470**	**−10.1 (−18.6, −1.58)**	**0.020**	258	−5.05 (−18.9, 8.77)	0.473	248	1.62 (−9.67, 12.92)	0.777
PCB 170	470	**−1.64 (−3.25, −0.04)**	**0.045**	258	−1.49 (−4.57, 1.597)	0.342	248	0.23 (−2.29, 2.74)	0.861
PCB 180	470	−0.52 (−1.08, 0.04)	0.070*	258	−0.65 (−1.97, 0.67)	0.336	248	0.14 (−0.94, 1.22)	0.793
PCB 183	470	−2.14 (−5.92, 1.64)	0.266	258	−12.8 (−28.5, 2.86)	0.109	248	−2.44 (−15.3, 10.4)	0.709
PCB 187	470	−0.81 (−1.95, 0.33)	0.164	258	−2.92 (−6.88, 1.04)	0.147	248	−0.33 (−3.58, 2.93)	0.843
PCB 99	470	−1.77(−3.91, 0.371)	0.105	258	−5.54 (−11.4, 0.27)	0.062*	248	−1.56 (−6.36, 3.25)	0.524
PCB 105	469	−11.3 (−27.4, 4.88)	0.171	257	−23.5 (−51.1, 4.07)	0.094	247	−6.04 (−28.7, 16.7)	0.601
∑DL-PCB	470	−1.58 (−3.49, 0.339)	0.105	258	−3.22 (−7.11, 0.67)	0.105	248	−0.69 (−3.89, 2.52)	0.672
OCP (ug/kg lipid)									
∑OCP	470	−0.04 (−0.09, 0.03)	0.266	258	−0.18 (−0.41, 0.05)	0.114	248	−0.05 (−0.24, 0.14)	0.597
Cis-Nonachlor	470	−3.17 (−6.45, 0.11)	0.058*	258	−4.91 (−10.6, 0.82)	0.092	248	−1.76 (−6.48, 2.97)	0.465
Hexachlorobenzene	470	**−2.04 (−4.04, −0.04)**	**0.046**	258	−1.62 (−4.49, 1.26)	0.269	248	−0.76 (−3.11, 1.60)	0.528
Mirex	470	−4.85 (−10.1, 0.40)	0.070*	258	−10.4 (−22.9, 2.13)	0.104	248	−1.71 (−12.0, 8.59)	0.744
Oxychlordane	470	−0.65 (−1.41, 0.11)	0.092	258	−1.79 (−3.63, 0.05)	0.056	248	−0.59 (−2.11, 0.93)	0.447
p,p′ DDE	470	−0.04 (−0.124, 0.05)	0.383	258	−0.27 (−0.68, 0.14)	0.190	248	−0.05 (−0.385, 0.29)	0.776
ß-HCH	468	−7.75 (−16.7, 1.19)	0.089	258	−12.5 (−28.5, 3.47)	0.124	248	−2.63 (−15.8, 10.6)	0.695
trans-Nonachlor	470	−0.32 (−0.74, 0.10)	0.138	258	−1.10 (−2.27, 0.08)	0.066*	248	−0.43 (−1.40, 0.54)	0.379
∑Legacy POP	470	−0.02 (−0.06, 0.01)	0.202	258	−0.10 (−0.23, 0.03)	0.130	248	−0.02 (−0.12, 0.09)	0.771
∑LipPOP	470	−0.02 (−0.06, 0.01)	0.203	258	−0.10 (−0.23, 0.03)	0.131	248	−0.02 (−0.12, 0.09)	0.769
PFAS (ng/mL serum)									
∑PFSA	477	−5.80 (−12.3,0.71)	0.081	266	−5.32 (−13. 6, 2.93)	0.205	256	−4.9 (−11.70, 1.78)	0.149
PFHxS	477	−82.9 (−176, 9.78)	0.079	266	−64.7 (−201, 72.0)	0.352	256	5.65 (−107, 119)	0.922
PFHpS	477	**−386 (−698, −74.9)**	**0.015**	266	−298 (−713, 117)	0.158	256	−269 (−608, 69.6)	0.119
PFOS	477	−6.07 (−13.1, 0.95)	0.090	266	−5.57 (−14.3, 3.17)	0.211	256	−5.47 (−12.6, 1.67)	0.133
∑PFCA	477	−4.38 (−15.8, 7.05)	0.452	266	−4.79 (−19.0, 9.42)	0.508	256	−10.2(−21.83, 1.45)	0.086
PFOA	477	−46.3 (−113, 20.1)	0.171	266	−27.3 (−127, 72.0)	0.588	**256**	**−119 (−202, −36.6)**	**0.005**
PFNA	477	−49.3 (−105, 6.12)	0.081	266	−39.3 (−111, 31.8)	0.277	256	−39.2 (−97.2, 18.9)	0.185
PFDA	477	−29.9 (−103, 42.8)	0.420	266	−20.6 (−104, 62.8)	0.627	256	−27.0 (−95.2, 41.3)	0.437
PFUnA	477	−6.52 (−28.6, 15.5)	0.562	266	−8.55 (−33.5, 16.4)	0.500	256	−11.4 (−31.8, 9.00)	0.271
∑PFAS	477	−3.13 (−7.53, 1.27)	0.163	266	−3.03 (−8.49, 2.43)	0.275	256	−3.66 (−8.11, 0.80)	0.107

n = number of participants having information for the parameter.
β = Linear regression coefficient in grams. CI = Confidence interval. Significant values p ≤ 0.05 are given in bold.
[a] Core adjustment: Adjusted for maternal age, plasma cotinine, parity, alcohol consumption during pregnancy and pre-pregnancy BMI.
[b] Core adjustment + gestational age at birth.
* Borderline significant values $p \leq 0.08$.

mainly had high factor loading for PBDEs which explained 7.22% of the total variation in the original POP concentrations. The fourth principal component (PC-4) mainly consisted of PFTrA and PFDoA and explained 5.35% of the total variation in the original POP concentrations. α- Chlordane, PBB 153, PCB 28 and PBDE 153 comprised the fifth principal component (PC-5) and explained 5.17% of the total variation in the original POP concentrations. The sixth principal component (PC-6) had high factor loading for PFOA and PFHpA and explained 4.00% of the total variation in the original POP concentrations. The six components together accounted for 84.26% of the total variance of POPs (Table S11 and S12).

As shown in Supplementary Table S13, after adjustment of age, BMI, parity, cotinine, alcohol consumption during pregnancy and GA at birth, most of the identified principal components inversely associated to foetal growth indices, although not significantly for birth weight and birth length. However, PC-1 (dominated by PCBs and OCPs) were positively associated with head circumference (adjusted $\beta = 0.39$, $p = 0.035$), while an inverse association were seen for PC-6 (PFOA and PFHpA, adjusted $\beta = -0.21$, $p = 0.038$) (Table S13).

PC-3 (PBDEs), PC-4 (PFTrA and PFDoA) and PC-6 (PFOA and PFHpA) significantly, positively associated with GA at birth. However, PC-1, dominated with most PCBs and OCPs, significantly inversely associated with GA at birth (Table S13).

The logistic regression analysis showed that PC-3 mainly comprised of PBDEs positively associated with the risk of low birth weight (adjusted OR = 3.60, $p = 0.017$, data not shown). A borderline inverse association between component of PFOA and PFHpA (PC-6) and preterm birth (adjusted OR = 0.42, $p = 0.065$) was observed (data not shown).

4. Discussion

The study present data and serum levels of POPs of 504 Inuit pregnant women from all five regions in Greenland sampled between 2010 and 2011 and 2013–2015. Baseline characteristics were similar across the regions, but we found a higher smoking prevalence in the East and North region. Smokers had significant higher plasma cotinine levels compared to non-smokers ($p < 0.0001$). The plasma cotinine for some non-smokers were higher than the detection limit indicating that some of the mothers were either not honest about their smoking status or that they had been exposed to passive smoking. The women from the East region also had higher parity than the other regions.

For the exposure levels of POPs, significant differences was observed between the regions with higher levels in the East and North regions. This could be caused by a higher reliance on traditional diet, consisting of marine mammals, and higher POP levels in the food items causing higher exposure to POPs (Long et al., 2015). It could also be due to the higher smoking prevalence we found in these regions (Knudsen et al., 2015; Long et al., 2015; Terkelsen et al., 2018).

The birth outcome characteristics were similar for all regions. Mean GA at birth for all regions were 39 weeks and mean birth weight for all regions were 3575 g.

Twenty-eight children were born before week 37, and are therefore categorized as preterm being 12.1% North >7.0% Disko Bay >5.3% East >5.1% West and > 2.3% South. The majority of the preterm infants ($n = 18$) were born in week 36. Knowing that the birth week is an important factor for foetal growth, preterm birth might be a potential

Table 7
Linear regression analysis of the associations between serum level of POPs and gestational age at birth (week).

	Unadjusted			Adjusted[a]		
	n	β (95% CI)	p-Value	n	β (95% CI)	p-Value
PCB (ug/kg lipid)						
∑PCB	453	−3e−4 (−0.001, 1e−4)	0.111	248	**−0.001 (−0.002, −1e−4)**	**0.042**
PCB 118	453	−0.01 (−0.02, 0.002)	0.122	248	**−0.02 (−0.04, −0.001)**	**0.037**
PCB 138	453	−0.001 (−0.004, 0.001)	0.234	248	**−0.006 (−0.01, −2e−4)**	**0.042**
PCB 153	453	−0.001 (−0.002, 0.003)	0.636	248	**−0.003 (−0.005,. −0.002)**	**0.033**
PCB 156	453	**−0.03 (−0.06, 0.001)**	**0.042**	248	−0.03 (−0.07, 0.02)	0.237
PCB 170	453	−0.006 (−0.01, 2e−4)	0.057*	248	−0.01 (−0.02, 0.002)	0.103
PCB 180	453	−0.002 (−0.004, 2e−4)	0.073*	248	−0.003 (−0.007, 5e−4)	0.085
PCB 183	453	−0.01 (−0.03, 0.006)	0.223	248	**−0.05 (−0.09, −0.001)**	**0.045**
PCB 187	453	−0.003 (−0.008, 0.001)	0.173	248	−0.01 (−0.02, 0.001)	0.063*
PCB 99	453	−0.01 (−0.02, 0.001)	0.073	248	**−0.02 (−0.04, −0.002)**	**0.027**
PCB 105	452	−0.06 (−0.12, 0.004)	0.068*	247	**−0.09 (−0.17, −0.008)**	**0.032**
∑DL-PCB	453	−0.01 (−0.02, 0.001)	0.073	248	**−0.01 (−0.02, −5e−4)**	**0.041**
OCP (ug/kg lipid)						
∑OCP	458	−1e−4 (−4e−4,1e−4)	0.306	248	−0.001 (−0.001, 1e−4)	0.073
Cis-Nonachlor	458	−0.01 (−0.03, 0.001)	0.074*	248	−0.02 (−0.03, 0.002)	0.084
Hexachlorobenzene	458	−0.006 (−0.01, 0.002)	0.121	248	−0.005 (−0.01, 0.004)	0.291
Mirex	458	−0.02 (−0.04, 0.001)	0.065*	248	**−0.04 (−0.08, −0.004)**	**0.030**
Oxychlordane	458	−0.002 (−0.005, 0.001)	0.152	248	**−0.006 (−0.01, −4e−4)**	**0.037**
p,p′ DDE	458	−2e−4 (−0.001, 0.0002)	0.415	248	−0.001 (−0.002, 2e−4)	0.103
ß-HCH	455	−0.03 (−0.06, 0.007)	0.113	248	**−0.05 (−0.09, −1e−4)**	**0.050**
trans-Nonachlor	458	−0.001 (−0.003, 0.001)	0.208	248	−0.003 (−0.007, 3e−4)	0.080
∑Legacy POP	458	−1e−4 (−3e−4, 1e−4)	0.209	248	**−4e−4 (−0.001, −2e−6)**	**0.049**
∑LipPOP	458	−1e−4 (−3e−4,1e−4)	0.210	248	**−4e−4 (−0.001, −8.48e−8)**	**0.050**
PFAS ng/mL serum						
∑PFSA	460	−0.01 (−0.03, 0.02)	0.554	256	−3e−4 (−0.02, 0.02)	0.979
PFHxS	460	−0.23 (−0.55, 0.09)	0.165	256	−0.32 (−0.718, 0.08)	0.113
PFHpS	460	−0.54 (−1.60, 0.52)	0.314	256	−0.15 (−1.34, 1.05)	0.811
PFOS	460	−0.006 (−0.03, 0.02)	0.609	256	0.001 (−0.02, 0.03)	0.937
∑PFCA	460	0.02 (−0.02, 0.06)	0.287	256	0.03 (−0.01, 0.07)	0.167
PFOA	460	0.18 (−0.04, 0.40)	0.106	256	**0.45 (0.17, 0.74)**	**0.002**
PFNA	460	−0.03 (−0.22, 0.16)	0.777	256	0.002 (−0.20, 0.21)	0.988
PFDA	460	0.01 (−0.24, 0.25)	0.953	256	0.03 (−0.21, 0.27)	0.779
PFUnA	460	0.01 (−0.06, 0.08)	0.807	256	0.02 (−0.05, 0.09)	0.628
∑PFAS	460	1e−4 (−0.02,0.02)	0.987	256	0.004 (−0.01, 0.02)	0.608

n = number of participants having information for the parameter.
β = Linear regression coefficient in weeks.
CI = Confidence interval.
Significant values p ≤ 0.05 are given in bold.
[a] Core adjustment: Adjusted for maternal age, plasma cotinine, parity, alcohol consumption during pregnancy and pre-pregnancy BMI.
* Borderline significant p ≤ 0.08.

confounder. Therefore, we also adjusted for GA when analysing relationships between exposure and birth outcome. We also stratified for term birth, and only analysed those born to term and this did not change our results and data is therefore only shown in the supplementary Tables S8 to S10.

Age, plasma cotinine and n−3/n−6 ratio were all positively correlated with the lipophilic POPs. The long half-lives and poor elimination of these chemicals result in an accumulation in the body over a lifespan. P-cotinine is a known biomarker for smoking and the significant association we observed are consistent with previous studies (Eslami et al., 2016; Moon et al., 2017). All measured POPs, both lipophilic PCBs, OCPs and PBDEs and the amphiphilic PFASs were positively associated with the sea food intake biomarker n−3/n−6 ratio, supporting the suggestion that the traditional food sources (marine mammals) are a source of POPs.

PFOA was the only congener that consistently showed significant association to all birth outcomes. The mean birth weight decreased significantly by 119 g per ng/mL increase in PFOA, while the length deceased borderline significantly by 0.37 cm ($p = 0.061$), the head circumference deceased significantly by 0.35 cm and a significant increase in GA 0.45 week, was observed.

Previous studies have found similar associations for PFOA and birth weight (Apelberg et al., 2007; Chen et al., 2012; Cao et al., 2018), but other studies did not report this association (Darrow et al., 2013; Bach et al., 2016). The reason for this inconsistency in results could be because numerus factors such as lifestyle have an impact on foetal growth, which have not yet been studied. The reported studies were conducted on population groups from different countries with conditions of life might differ, that could possibly affect foetal growth, vary from each other. We evaluated potential confounders by adjusting for income and educational level but found no significant associations. When stratifying for child gender, the female children the PFOA remained inversely and significantly associated with birth weight (−161 g/ng/mL PFOA) and head circumference (−0.51 cm/ng/mL PFOA), indicating that PFOA might affect the foetal growth by disturbances in sex homeostasis. For the male children, we, however, found a non-significant inverse association. This indicates that PFOA still affected the male children but not enough to meet the statistical requirements. Surprisingly, we saw a positive association between PFOA and gestation age including both genders (β = 0.45 week, ρ = 0.002) (Table 7), for females only (β = 0.48 week, $p = 0.019$) and for males only (β = 0.42 week, $p = 0.043$, Table S7) being in contrast since most of the associations we found were negative. An explanatory hypothesis could be that the mother's body is trying to prolong the GA to compensate for the lower birth weight caused by PFOA exposure.

For the lipophilic POPs, most of the results were non-significant for birth weight, birth length and head circumference. We did, however, see an inversely significant association between PCB 99 and PCB105 (borderline) and birth length for core adjustment disappearing upon GA adjustment (Table S2). Several of the lipophilic POPs were significantly inverse associated with GA at birth (Table 7). The association between PCB 99 and birth length were not seen after stratifying for child

gender (Table S5), but several of the POP exposure associations with GA at birth remained significant in female children (Table S7), which suggesting that female offspring are more sensitive to POP exposure than male offspring, possibly due to disturbances in the sex homeostasis.

Ponderal Index (PI), including weight and length related parameters, might also give indices for foetal growth. We further calculated PI as [(birth weight in gram/(birth length in cm))^3 × 100] (MedicalBiostatistics.com, n.d.) and assessed the association of POPs and PI. We observed that PFASs such as PFHxS, PFHpS, PFOS, PFOA and ΣPFASs were significantly, inversely associated with PI, but the associations attenuated upon adjustment of covariates, which might be related the reduced sample size.

The reason why we found few significant associations for the lipophilic POPs could be because the detected levels are lower than previously found (Deutch et al., 2004; Deutch et al., 2007a, 2007b; Bjerregaard et al., 2013). This could be caused by a reduced intake of the Greenlandic traditional food, which is the main source of the lipophilic POPs (Bjerregaard et al., 2001). The traditional food is slowly being replaced by more westernized food sources, and the traditional food now only make up approximately 20% or less of the food intake (Deutch et al., 2007a, 2007b; Jeppesen and Bjerregaard, 2012; Knudsen et al., 2015; Terkelsen et al., 2018). Furthermore, the regulation of legacy POPs has helped to reduce the use and emission of these chemicals. These factors contribute to a reduced POP exposure of the Greenlandic people, which correlates with a lower exposure level presented in this manuscript compared to earlier reports (Deutch et al., 2007a, 2007b, Bjerregaard et al., 2013). This indicates that the regulatory measures have a decreasing impact on the environmental pollution by POPs. However, it is important to also include research in the combined exposure of both legacy POP and the less regulated PFASs (Kruger et al., 2008; Bonefeld-Jorgensen, 2010; Bjerregaard-Olesen et al., 2019; Long et al., 2019). To assess the actual effect of POP mixtures, we performed the principle component analysis (PCA) and observed the identified components showed similar and even stronger associations with birth outcomes compared with single POP congeners. The overall trend of our analysis was inverse associations between prenatal POP exposure and birth outcome, indicating that POPs exposure have a negative effect on foetal growth. POPs cross the placental barrier and are also passed on to the infant by breast feeding (van den Berg et al., 2017). Thus POPs can have a negative effect on the infant in the postnatal breastfeeding period and the negative health effects can thus appear later in life. Therefore, it is important to further examine the effects of POPs in childhood and later in life. Studies have already been conducted on this area, finding a relationship between POPs and cognitive deficits and motor function (Berghuis et al., 2018), metabolic disturbances (Tang-Peronard et al., 2015; Lauritzen et al., 2018) and hormonal disturbances (Garcia-Villarino et al., 2018). To further study these relationships the ACCEPT cohort is currently followed up in the BioSund-ACCEPT project until the age of 3–5 and 7–8 years of age.

There are some limitations in the presented study. As given in Fig. 2, 504 women met our inclusion criteria and were included in the statistical analysis. Unfortunately, not all the required data were obtained for all the women, meaning that some were not included in the analysis. That was for the most part information on our chosen core adjustments: plasma cotinine, mother age, parity, alcohol consumption during pregnancy and pre-pregnancy BMI. Thus when analysing the associations between exposure and outcome for the adjusted data, the full number of 504 participants were not included in all analysis, weakening the statistical power.

5. Conclusion

The exposure levels of POPs in the ACCEPT Greenlandic pregnant women during 2010–2015 were lower than previously reported (Bjerregaard et al., 2013; Long et al., 2015; Knudsen et al., 2015). This indicates a decreasing POP exposure trend over time although the POP levels are still one of the highest global wide. We found a regional difference in exposure levels, being highest in the North and East region, supporting that traditional marine diet is still a major source of POPs. We found significant inverse associations between PFOA and birth outcome indices, which were only significant among female offspring after stratification for gender. In contrast, a positive significant association between PFOA and GA was also found for both female and male children. Although in general a negatively association with foetal growth indices', the lipophilic POP showed no convincing significance. However, in contrast to PFOA, several of the lipophilic POPs were significantly inversely associated with GA. Our data indicate that POPs are still of concern for foetal growth and health for the coming generation in Greenland.

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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.2019.134118.

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