HHS Public Access

Author manuscript

Environ Int. Author manuscript; available in PMC 2020 February 14.

Published in final edited form as:

Environ Int. 2019 September ; 130: 104929. doi:10.1016/j.envint.2019.104929.

Perfluoroalkyl and polyfluoroalkyl substances and fetal thyroid hormone levels in umbilical cord blood among newborns by prelabor cesarean delivery

Ruxianguli Aimuzi[a,b,1], **Kai Luo**[a,b,1], **Qian Chen**[b], **Hui Wang**[a], **Liping Feng**[b,c], **Fengxiu Ouyang**[b,*], **Jun Zhang**[a,b,*]

[a]School of Public Health, Shanghai Jiao Tong University, Shanghai, 200025, China.

[b]Ministry of Education-Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital, Shanghai Jiao-Tong University School of Medicine, Shanghai, 200092, China.

[c]Department of Obstetrics and Gynecology, Duke University School of Medicine, Durham, North Carolina, USA.

Abstract

Background: Perfluoroalkyl and polyfluoroalkyl substances (PFAS) have been reported to disrupt the thyroid function. But epidemiological evidence on the association between PFAS and thyroid hormone (TH) levels in cord blood is scarce and controversial. We aimed to examine the association between cord blood PFAS concentrations and TH levels in prelabor caesarean deliveries.

Methods: We measured ten PFAS and three THs in cord blood in 568 prelabor caesarean deliveries. The associations between PFAS and TH levels were examined using multiple linear regression model and sparse partial least square (SPLS) regression model.

Results: In SPLS analyses, thyroid stimulating hormone (TSH) level decreased with increasing concentrations of perfluorooctane sulfonate (PFOS, β= −0.012, 95% confidence interval [CI]: −0.019, −0.005), perfluorononanoic acid (PFNA, β= −0.012, 95% CI: −0.019, −0.005), perfluorodecanoic acid (PFDA, β= −0.012, 95% CI: −0.02, −0.005), perfluoroundecanoic acid (PFUA, β= −0.013, 95% CI: −0.021, −0.006) and perfluorododecanoic acid (PFDoA, β= −0.013, 95% CI: −0.023, −0.006). Moreover, we found a positive association between PFDoA and free thyroxine (FT4) levels (β= 0.190, 95% CI: 0.063, 0.304) after adjusting for potential confounders. Free tri-iodothyronine (FT3) levels were positively associated with concentrations of PFOS (β= 0.059, 95% CI: 0.023, 0.100), but negatively associated with PFDoA (β= −0.153, 95% CI: −0.212, −0.106). We also observed gender disparity in the associations of PFAS exposure and FT3, FT4, TSH levels.

Conclusion: Our results suggest that prenatal exposure to certain PFAS may disrupt fetal thyroid function. The effect may be gender-specific.

---

[1]These two authors have contributed equally and, therefore, are considered as co-first authors.
[*]These two authors are considered as co-corresponding authors.

Conflict of interest
The authors disclaimed no conflict of interest.

Keywords

Perfluoroalkyl substances; Thyroid hormones; Cord blood; Caesarean delivery; Spare partial least square (SPLS) regression

1. Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are synthetic fluorine-containing compounds that have been extensively used in various consumer products including surfactants, cookware, lubricants, clothing, and food packaging since the 1950s (Lindstrom et al. 2011). Due to the strong carbon-fluorine bond, PFAS, in particular for those with long-carbon chain, such as perfluorooctane sulfonate [PFOS] perfluorooctanoate [PFOA] and perfluorohexane sulfonate (PFHxS), can persist in the environment and human body for a long time, with estimated half-lives of 7.3 years for PFHxS, 4.8years for PFOS and 3.5 years for PFOA in human serum (Olsen et al. 2007). The general population is exposed to PFAS mainly through packaged food, water, household dust and air inhalation (Wang et al. 2014). The persistence and widespread use of some PFAS has resulted in ubiquitous human exposure (Calafat et al. 2007). Evidence shows that PFAS can cross the placental barrier and interfere fetal thyroid hormone (TH) homeostasis (Shah-Kulkarni et al. 2016; Tsai et al. 2017; Yang et al. 2016) , while the latter is crucial for fetal growth and development (Forhead and Fowden 2014; Shields et al. 2011)

Experimental studies found that PFOS treatment resulted in lowered thyroxine (T4) and triiodothyronine (T3) levels in pregnant rats, and decreased total T4 level in rat pups (Luebker et al. 2005; Thibodeaux et al. 2003). In humans, the association between cord blood PFAS and offspring THs was less certain. Studies performed by Shah-Kulkarni et al. in Korea, Yang et al. in Beijing and de Cock et al. in Netherlands found positive associations between cord blood PFAS and fetal T4 levels while a cohort study in Taiwan reported negative associations(de Cock et al. 2014; Shah-Kulkarni et al. 2016; Tsai et al. 2017; Yang et al. 2016). Another study in Korea did not find an association of prenatal PFAS exposure with TH levels (Kim et al. 2011). This may be partly attributable to the time when THs were measured and how the fetus was delivered. A neonatal TSH surge occurs at delivery, leading to a subsequent increase in T3 and T4 production (Stoffer 2008), which creates challenges in assessing the true association between PFAS exposure and TH levels at birth. Furthermore, babies born vaginally had statistically significantly higher umbilical cord plasma TSH but similar T4 concentrations to babies born by caesarean section (Gupta et al. 2014; Lao and Panesar 1989). This phenomenon may be related to intrapartum fetal stress even though much of the stress is physiological (Armanian et al. 2013), leading to rapid changes of TH levels until shortly after birth (Stoffer 2008).

Keeping these potential challenges in mind, we examined the association between PFAS and THs in the cord blood among prelabor cesarean deliveries. Moreover, prior studies mainly relied on conventional regression approach to examine the effects of PFAS in isolate, leaving the residual confounding by co-exposed, highly correlated PFAS components uncontrolled. Thus, we used sparse partial least squares (SPLS) regression modeling (Chun and Keles

2010), a recently introduced multipollutant model, to assess the associations between PFAS and TH levels in the cord blood.

2. Methods

2.1 Study design and participants

Between 2012 and 2013, the Shanghai Obesity and Allergy Cohort Study recruited 1244 pregnant women from two large tertiary-level maternity hospitals in Shanghai, China. Information on demographic characteristics, including fish intake, maternal education level, smoking status and alcohol consumption, was collected by trained nurses through a face-to-face questionnaire interview at enrollment. Medical information, such as maternal age, pre-pregnancy body mass index (BMI), gestational age, infant sex, thyroid disease before and during pregnancy, and mode of delivery, was retrieved from medical records. 441 subjects were excluded because of the lack of information on PFAS or TH measurements in the cord blood. Among 803 infant-mother pairs, 637 gave birth by caesarean section. 20 subjects were excluded due to a history of or current thyroid diseases and 16 subjects for lack of information on maternal thyroid function. In addition, 20 subjects were excluded for intrapartum cesarean delivery and 13 were excluded for preterm birth. Thus, 568 subjects were included in the final analysis (details of participant recruitment and reasons for caesarean section were described in the supplementary materials Figure S1, Table S1).

The cord blood collected at delivery was stored at −80℃ until testing. We obtained a signed informed consent from all participants and the study was approved by the institutional review board of both hospitals.

2.2 Exposure assessment

Ten PFAS were measured in cord plasma using liquid chromatograph system coupled with tandem mass spectrometry (HPLC-MS/MS, Agilent 1290 – 6490, Agilent Technologies Inc., USA). These compounds included PFOA, PFOS, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUA), PFHxS, perfluorododecanoic acid (PFDoA), perfluorobutane sulfonate (PFBS), perfluorooctane sulfonamide (PFOSA), perfluoroheptanoic acid (PFHpA). Detailed methods of PFAS measurements have been described previously (Wang et al. 2016). The limits of detection (LOD) for PFAS ranged from 0.009 to 0.12 ng/mL. PFOSA and PFHpA were detected in < 50% of the samples (46.0% and 19.5%, respectively), and thus were not included in further analyses; concentrations below the LOD were replaced by the LOD/√2 (Hornung and Reed 1990).

2.3 Assessment of thyroid hormones

FT3, FT4, TSH concentrations in cord blood serum were determined by chemiluminescent microparticle immunoassay using the Architect system (Abbott Laboratories, Abbott Park, IL, USA). Detailed methods of THs measurements have been described in our previous study (Wang et al. (2017). The LODs for FT3, FT4 and TSH were 1.54 pmol/L, 5.15 pmol/L and 0.35 mIU/L, respectively. TSH and FT4 were detected in > 99% of the samples, while FT3 could be detected in 82.4% of the samples. Concentrations below the LOD were

replaced by the LOD/√2. (Hornung and Reed 1990). QA/QC procedures were performed for all THs analyses in accordance with the Architect system.

2.4 Statistical analysis

Because of similar chemical structures and emission sources, PFAS are generally highly correlated. Analyzing the association between PFAS and THs in a one-at-a-time approach may fail to account for residual confounding by co-exposed PFAS component, which requires further adjustment. Although mutual-adjusted approach with all PFAS included in the same regression model can partially generate the adjusted estimates, it is only viable when the correlation among PFAS is weak to moderate. The inclusion of highly correlated PFAS in the regression model potentially introduces multi-collinearity, resulting in unstable estimates with inflated standard errors. To obtain the valid estimates of effects of PFAS on fetal TH levels, flexible multipollutant models that are good at handling issues of multi-collinearity are needed. Recently, sparse partial least square (SPLS) regression, a multipollutant model with the combination of properties of partial least square regression (PLS) and least absolute shrinkage and selection operator (LASSO) regression, has been introduced to assess the effects of multiple endocrine disrupting chemicals on reproductive function (Lenters et al. 2015). While PLS addresses the multi-collinearity by dimension reduction (i.e. finding the latent components of correlated predictors) in a supervised approach, LASSO renders the property of sparseness to SPLS to shrink the regression coefficients of correlated predictors toward to zero. A simulation study proved that SPLS has a good performance in variable selection, providing a good alternative method to identify the dominant pollutant related to the outcome of interest (Lenters et al. 2018). Therefore, we adopted the SPLS regression to address this issue and identify PFAS that are associated with the THs in newborns.

In present study, SPLS enables the matrix of PFAS (exposure) and THs (outcome) vector to be simultaneously decomposed into latent variables and regressed in a way that maximizes the covariance between exposures and outcome, and the penalization is applied during this dimension reduction. Specifically, L1 penalty of LASSO was approximated via the SPLS sparsity penalty, which performs the variable selection (Chun and Keles 2010). And the regression coefficients of PFAS were obtained via PLS for the reduced set of PFAS matrix. In this context, the model complexity depends on the number of components (k) used to construct the model and the degree of sparsity (η). We created a series of SPLS models with varied value of k (from 1 to 8 based on the numbers of PFAS) and η (from 0.01 to 0.99 in steps of 0.01). The final combination of k and η was determined by the 10-fold cross-validation with each model ran for 100 times and the overall minimum mean squared prediction error (Chun and Keles 2010). Further, the 95% confidence interval (CI) of coefficients was obtained via bootstrapping with 1000 iterations. The interpretation and discussion of the results will be based mainly on the SPLS results.

Since there is no simple way to adjust for potential confounders in a regression that performs variable selection, a two-stage regression approach was adopted: each TH and each PFAS measurement were separately regressed on potential confounders by conventional regression and, then, SPLS regression models were fitted based on the generated residuals (Xing et al.

2011). A set of covariates were selected according to previous studies including maternal age, infant sex, parity (nulliparous or parous), gestational age at delivery, maternal pre-pregnancy BMI and maternal fish consumption during pregnancy. As only few women drank alcohol (1.9%) and smoked during pregnancy, variables of maternal drinking and smoking status were not included in the final adjusted model.

In order to assess the gender specific effects, we conducted a series of stratified analyses according to infant gender by adopting the above modeling strategies. Because FT3 was only detected in 82.4% of samples, we reexamined the association between PFAS and FT3 by limiting the analysis to subjects with FT3 levels above LOD to assess the robustness of our main findings. We performed additional sensitivity analyses among first-born infants to assess the potential impact of previous children on PFAS levels.

Before regression modeling, PFAS were natural log-transformed to address their right-skewed distribution. Of three indicators of THs, only TSH was log-transformed because of its right-skewed distribution. We also mean-centered all log-transformed PFAS and scaled them by dividing one time of their respective standard deviation, equivalent to a z-score. All the scaled PFAS and THs were modeled as continuous variables.

Estimates were presented as changes in TH levels per unit increase in PFAS. All the analyses were performed through RStudio version 1.1.453 (2009–2018 RStudio, Inc) and the SPLS analyses were performed via “spls” package (Chung et al. 2013). Spearman's rank correlations were used to assess unadjusted relationships among PFAS. Statistical significance level was set at 0.05 for two sides.

3. Results

Table 1 presents the demographic characteristics of the study population. Participants had an average age of 29.6 years and a mean pre-pregnancy BMI of 21.8kg/m^2. Most participants in the study tended to be well educated and 89.1% of women were nulliparous. Only one woman smoked during pregnancy and eleven women consumed alcohol during pregnancy. The mean gestational age was 38.8 weeks and 53.8% of the infants were male. The mean birth weight was 3450 g and mean birth length was 49.9 cm.

Table 2 summarizes the distribution of PFAS and THs in cord blood. The highest median concentration was 7.57ng/mL for PFOA, followed by PFOS (2.51ng/mL), PFNA (0.66ng/mL), PFDA (0.41ng/mL), PFUA (0.40ng/mL), PFHxS (0.18ng/mL), PFDoA (0.11ng/mL), and PFBS (0.05ng/mL). As expected, some PFAS were highly correlated, with Spearman correlation coefficient ranging from 0.019 to 0.888 (see Table S2). The median concentrations of FT3, FT4 and TSH were 2.03pmol/L, 13.48pmol/L, and 4.66mIU/L, respectively. Cord blood concentrations of PFAS and THs showed no significant differences by sex.

We examined the associations between THs and PFAS levels in cord blood through single-pollutant, mutual-adjusted (Table S3-S6) and SPLS regression models. In general, the direction of associations for PFAS selected in SPLS models was consistent with that in single and multi-pollutant linear regression analyses (Tables S3-S6). Due to the multi-

collinearity problem in the multiple linear regression, our discussion and explanation in this study were mainly based on results from SPLS analyses.

Table 3 presents the associations between PFAS and FT4 levels in the cord blood of all infants. A standardized unit increase in PFDoA was significantly associated with 0.190 pmol/L (95% CI: 0.063, 0.304) increase in FT4 levels. Further, we conducted stratified analyses by gender. SPLS models showed that PFOA (β= 0.062, 95% CI: 0.024, 0.138), PFNA (β= 0.04, 95% CI: 0.006, 0.081), PFDA (β= 0.043, 95% CI: 0.016, 0.078) and PFBS (β= 0.056, 95% CI: 0.009, 0.158) were positively associated with FT4 among boys while PFDoA was positively associated with FT4 in both boys and girls with the estimates of 0.054 pmol/L (95% CI: 0.019, 0.119) and 0.174 pmol/L (95% CI: 0.019, 0.331), respectively.

Regarding the relationship between PFAS and FT3 in cord blood among all infants (Table 3), PFOS (β= 0.059, 95% CI: 0.023, 0.100) was selected and positively associated with FT3, and PFDoA (β= −0.153, 95% CI: −0.212, −0.106) was found to be significantly reversely associated with FT3. Further stratified analyses by gender indicated that there were gender-specific effects in terms of the associations between PFAS and FT3 in cord blood. Specifically, we found that PFBS (β=0.098, 95% CI: 0.021, 0.182) was selected and positively associated with FT3 among boys. PFDoA was negatively associated with FT3 in both boys and girls but the estimates were stronger in boys.

Meanwhile, there were consistent negative associations between PFAS and TSH. Five of eight PFAS were identified and negatively associated with TSH (Table 3). In the stratification analysis by fetal sex, PFDoA was negatively associated with TSH in boys (β= −0.062, 95% CI: −0.108, −0.017) while PFOS (β= −0.016, 95% CI: −0.032, −0.002) showed a negative association in girls (Table 3).

Given the lower detection rate of FT3, we conducted a sensitivity analysis by selecting those with a level of FT3 above the LOD. Table S6 shows that the negative association between PFDoA and FT3 remained significant while the positive association between PFOS and FT3 disappeared. Further, a positive association of PFNA and a negative association of PFOA with FT3 emerged. The gender-specific analysis shows that PFNA was positively associated with FT3 while the positive association between the PFBS and FT3 disappeared among boys. PFDoA remained significantly inversely associated with FT3 in both boys and girls.

We performed another sensitivity analysis in only first-born babies (N=506) and found that the associations of selected PFAS with THs did not change appreciably (Table S7). When stratified by fetal sex, the direction of the association of PFAS with THs remained unchanged and the associations between PFNA, PFUA and TSH among girls became significant. Among boys, only PFDoA was still significantly and positively associated with FT4 but negatively associated with FT3. The negative association between PFBS and TSH became statistically significant.

4. Discussion

Our study explored the effects of *in utero* exposure to PFAS on fetal TH levels by assessing the associations between PFAS and THs in cord blood. We found a significant positive association of PFOS, a negative association of PFDoA with FT3, and a significant positive association of PFDoA with FT4. We also observed negative associations of PFAS with TSH. The estimates were significant except for PFOA, PFHxS and PFBS. Meanwhile, gender-specific effects of PFAS exposure were also observed.

The fetal period is a particularly vulnerable stage during which many critical neurodevelopmental events occur. THs are known to be crucial for fetal growth and neurodevelopment (Prezioso et al. 2018; Shields et al. 2011). Any disturbance of the homeostasis of maternal or fetal THs would result in adverse health effects, including low birth weight, metabolic disturbance or impaired neurodevelopment (Ajmani et al. 2014; Saki et al. 2015).

PFAS, especially those with short chains or carboxyl groups, are shown to be able to easily cross the placental barrier, exposing the fetus *in utero* (Monroy et al. 2008). As the thyroid toxicity of PFAS is indicated in adults and rodents, increasing attention has been drawn to the effects of prenatal exposure to PFAS on fetal TH levels (Ballesteros et al. 2017; Kim et al. 2018). To our knowledge, six studies assessed the association between cord blood PFAS and fetal TH levels (de Cock et al. 2014; Dufour et al. 2018; Kim et al. 2011; Shah-Kulkarni et al. 2016; Tsai et al. 2017; Yang et al. 2016) (see Table S8), and two of them adjusted for delivery method (Tsai et al. 2017; Yang et al. 2016), but none of them were restricted to cesarean deliveries.

Our study found that PFDoA was positively associated with fetal FT4. Dallaire et al. (2009) also observed a positive association between PFOS and FT4 in Inuit adults from Nunavik, Canada. Lin et al. (2013) found that PFNA was positively associated with FT4 levels in a cohort of adolescents and young adults from Taiwan (β=0.004, 95% CI: 0.001, 0.007). While these studies were consistent with ours, it should be pointed out that the association between PFAS and FT4 may differ between the fetus and adults. In contrast, Tsai et al. and Yang et al. observed no association between any PFAS and FT4 in cord blood (Tsai et al. 2017; Yang et al. 2016).

Likewise, in our study, PFOS was positively associated with FT3 and PFDoA was negatively associated with FT3. Yang et al. (2016) also found a positive association between PFOS and FT3 in cord blood. Two studies conducted among adult women reported that PFOS and PFNA (Byrne et al. 2018) and PFOA (Lewis et al. 2015) were positively associated with FT3. However, Tsai et al. (2017) observed no association between PFAS and FT3 in cord blood

Furthermore, our study showed that fetal TSH was negatively associated with most of PFAS in cord blood, which is inconsistent with previous studies by Kim et al. (2011), Tsai et al. (2017), and Yang et al. (2016). But it should be reminded that such a direct comparison may be difficult since our study population was restricted to prelabor caesarean deliveries only.

And the concentrations of most PFAS measured in these studies were generally lower than those in our study (Table S8). Further research on this association is needed.

To date, the exact underlying mechanisms of how PFAS affect THs remain unclear. Toxicological studies suggested several potential mechanisms. PFAS may competitively bind to thyroid-hormone binding proteins, such as the thyroxine-binding globulin (TGB), transthyretin (TTR), and albumins (Weiss et al. 2009). PFAS may also increase type 1 deiodinase concentrations, which may increase conversion of T4 to T3 (Yu et al. 2009). Increased FT3 and FT4 may, in turn, result in decreased TSH due to feedback loop through hypothalamic-pituitary-thyroid axis. However, these mechanisms cannot explain all the findings in this study since we also found that PFDoA can significantly reduce the level of FT3. We speculate that there might exist a PFAS-specific effect. PFDoA might activate the thyroidal type 3 deiodinase, which is involved in the inactivation of T4 and T3 in cells, resulting in a reduced level of FT3. Nonetheless, this hypothesis has not been corroborated in previous studies; the present study was not a causation study and there is discrepancy in the result of sensitivity analysis of FT3. The possibility of chance cannot be excluded, either. Therefore, the results should be considered as preliminary.

In addition, consistent with previous studies in adults, adolescents and infants, we also observed gender-specific effects of PFAS on fetal THs. Several studies suggested that estrogen or other sex hormones may affect thyroid homeostasis (D'Angelo and Fisher 1969; Kraiem et al. 1994). Moreover, toxicological studies showed that PFAS can promote estrogen dependent gene expression and alter concentrations of both estrogen and androgens (Sonthithai et al. 2016). However, the underlying mechanisms have yet to be fully elucidated.

Our study has several strengths. First, compared with previous studies, we used SPLS, a statistical method that combines the strengths of PLS and LASSO and is capable of variable selection under collinearity. This model is more flexible in addressing collinearity and identifying the dominant PFAS related to THs (Lenters et al. 2018) and represents an important step towards understanding how exposure to mixtures of PFAS may affect the fetal thyroid axis. Second, we measured both PFAS and THs in the cord blood. Given the fact that PFAS may exhibit various transfer ratios between maternal and fetal compartments (Monroy et al. 2008), PFAS levels measured in cord blood may more accurately reflect fetal exposure. Further, TSH cannot be transferred from the mother to the fetus through the placenta (Polak 2014). Therefore, TH levels measured in cord blood is a good representation of levels during fetal life. Finally, we examined the association between PFAS and THs in prelabor caesarean deliveries whose TH levels, particularly for TSH levels, are generally less affected by the long labor duration and delivery process.

The present study also has several limitations. First, our study is a cross-sectional analysis in nature and, therefore, the temporal relationship between PFAS and THs cannot be assured. However, some PFAS (e.g., PFOA, PFOS, PFHxS) are quite stable with a long half-life in plasma. Their levels are likely to reflect the exposure prior to the outcomes (Olsen et al. 2007). Second, several PFAS in our study have limited ranges, which may limit our ability to identify new associations. Third, we didn’t have the data regarding maternal TH

concentrations, which may also influence PFAS levels. Fourth, we didn't measure the fetal levels of total T3, total T4, thyroid transport proteins, thyroid peroxidase antibodies and iodine sufficiency, which would provide a clearer picture of this complex association. Finally, the observed association between PFAS and THs might be due to other confounding exposures that were not measured in the current study.

In conclusion, our study suggests that *in utero* PFAS exposure may be associated with fetal thyroid function. Considering the importance of THs in a rapidly developing fetus, this issue warrants further investigations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

This study was partly funded by the National Natural Science Foundation of China (81530086) and supported by National Human Genetic Resources Sharing Service Platform (2005DKA21300)

References

Ajmani SN; Aggarwal D; Bhatia P; Sharma M; Sarabhai V; Paul M Prevalence of overt and subclinical thyroid dysfunction among pregnant women and its effect on maternal and fetal outcome. Journal of obstetrics and gynaecology of India. 64:105–110; 2014

Armanian AM; Hashemipour M; Esnaashari A; Kelishadi R; Farajzadegan Z Influence of perinatal factors on thyroid stimulating hormone level in cord blood. Advanced biomedical research. 2:48; 2013 [PubMed: 24516848]

Ballesteros V; Costa O; Iniguez C; Fletcher T; Ballester F; Lopez-Espinosa MJ Exposure to perfluoroalkyl substances and thyroid function in pregnant women and children: A systematic review of epidemiologic studies. Environ Int. 99:15–28; 2017 [PubMed: 27884404]

Byrne SC; Miller P; Seguinot-Medina S; Waghiyi V; Buck CL; von Hippel FA; Carpenter DO Exposure to perfluoroalkyl substances and associations with serum thyroid hormones in a remote population of Alaska Natives. Environmental research. 166:537–543; 2018 [PubMed: 29958161]

Calafat AM; Kuklenyik Z; Reidy JA; Caudill SP; Tully JS; Needham LL Serum concentrations of 11 polyfluoroalkyl compounds in the u.s. population: data from the national health and nutrition examination survey (NHANES). Environmental science & technology. 41:2237–2242; 2007 [PubMed: 17438769]

Chun H; Keles S Sparse partial least squares regression for simultaneous dimension reduction and variable selection. Journal of the Royal Statistical Society Series B, Statistical methodology. 72:3–25; 2010 [PubMed: 20107611]

Chung D; Chun H; Keles S spls: Sparse Partial Least Squares (SPLS) Regression and Classification. R Package; 2013

D'Angelo SA; Fisher JS Influence of estrogen on the pituitary-thyroid system of the female rat: mechanisms and loci of action. Endocrinology. 84:117–122; 1969 [PubMed: 4881996]

Dallaire R; Dewailly E; Pereg D; Dery S; Ayotte P Thyroid function and plasma concentrations of polyhalogenated compounds in Inuit adults. Environmental health perspectives. 117:1380–1386; 2009 [PubMed: 19750101]

de Cock M; de Boer MR; Lamoree M; Legler J; van de Bor M Prenatal exposure to endocrine disrupting chemicals in relation to thyroid hormone levels in infants - a Dutch prospective cohort study. Environmental health : a global access science source. 13:106; 2014 [PubMed: 25495114]

Dufour P; Pirard C; Seghaye MC; Charlier C Association between organohalogenated pollutants in cord blood and thyroid function in newborns and mothers from Belgian population. Environmental pollution (Barking, Essex : 1987). 238:389–396; 2018

Forhead AJ; Fowden AL Thyroid hormones in fetal growth and prepartum maturation. J Endocrinol. 221:R87–r103; 2014 [PubMed: 24648121]

Gupta A; Srivastava S; Bhatnagar A Cord blood thyroid stimulating hormone level--interpretation in light of perinatal factors. Indian pediatrics. 51:32–36; 2014 [PubMed: 24277962]

Hornung RW; Reed LD Estimation of Average Concentration in the Presence of Nondetectable Values. App Occup Env Hyg. 5:46–51; 1990

Kim MJ; Moon S; Oh BC; Jung D; Ji K; Choi K; Park YJ Association between perfluoroalkyl substances exposure and thyroid function in adults: A meta-analysis. PLoS One. 13:e0197244; 2018 [PubMed: 29746532]

Kim S; Choi K; Ji K; Seo J; Kho Y; Park J; Kim S; Park S; Hwang I; Jeon J; Yang H; Giesy JP Trans-placental transfer of thirteen perfluorinated compounds and relations with fetal thyroid hormones. Environmental science & technology. 45:7465–7472; 2011 [PubMed: 21805959]

Kraiem Z, .; Sadeh O, .; Blithe DL; Nisula BC Human chorionic gonadotropin stimulates thyroid hormone secretion, iodide uptake, organification, and adenosine 3',5'-monophosphate formation in cultured human thyrocytes. Journal of Clinical Endocrinology & Metabolism. 79:595; 1994 [PubMed: 8045981]

Lao TT; Panesar NS Neonatal thyrotrophin and mode of delivery. British journal of obstetrics and gynaecology. 96:1224–1227; 1989 [PubMed: 2487997]

Lenters V; Portengen L; Smit LA; Jonsson BA; Giwercman A; Rylander L; Lindh CH; Spano M; Pedersen HS; Ludwicki JK; Chumak L; Piersma AH; Toft G; Bonde JP; Heederik D; Vermeulen R Phthalates, perfluoroalkyl acids, metals and organochlorines and reproductive function: a multipollutant assessment in Greenlandic, Polish and Ukrainian men. Occupational and environmental medicine. 72:385–393; 2015 [PubMed: 25209848]

Lenters V; Vermeulen R; Portengen L Performance of variable selection methods for assessing the health effects of correlated exposures in case-control studies. Occupational and environmental medicine. 75:522–529; 2018 [PubMed: 28947495]

Lewis RC; Johns LE; Meeker JD Serum Biomarkers of Exposure to Perfluoroalkyl Substances in Relation to Serum Testosterone and Measures of Thyroid Function among Adults and Adolescents from NHANES 2011–2012. Int J Environ Res Public Health. 12:6098–6114; 2015 [PubMed: 26035660]

Lin CY; Wen LL; Lin LY; Wen TW; Lien GW; Hsu SH; Chien KL; Liao CC; Sung FC; Chen PC; Su TC The associations between serum perfluorinated chemicals and thyroid function in adolescents and young adults. Journal of hazardous materials. 244–245:637–644; 2013

Lindstrom AB; Strynar MJ; Libelo EL Polyfluorinated compounds: past, present, and future. Environmental science & technology. 45:7954–7961; 2011 [PubMed: 21866930]

Luebker DJ; York RG; Hansen KJ; Moore JA; Butenhoff JL Neonatal mortality from in utero exposure to perfluorooctanesulfonate (PFOS) in Sprague-Dawley rats: dose-response, and biochemical and pharamacokinetic parameters. Toxicology. 215:149–169; 2005 [PubMed: 16129535]

Monroy R; Morrison K; Teo K; Atkinson S; Kubwabo C; Stewart B; Foster WG Serum levels of perfluoroalkyl compounds in human maternal and umbilical cord blood samples. Environmental research. 108:56–62; 2008 [PubMed: 18649879]

Olsen GW; Burris JM; Ehresman DJ; Froehlich JW; Seacat AM; Butenhoff JL; Zobel LR Half-life of serum elimination of perfluorooctanesulfonate,perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environmental health perspectives. 115:1298–1305; 2007 [PubMed: 17805419]

Polak M Human fetal thyroid function. Endocrine development. 26:17–25; 2014 [PubMed: 25231441]

Prezioso G; Giannini C; Chiarelli F Effect of Thyroid Hormones on Neurons and Neurodevelopment. Hormone research in paediatrics. 90:73–81; 2018 [PubMed: 30157487]

Saki F; Dabbaghmanesh MH; Ghaemi SZ; Forouhari S; Omrani GR; Bakhshayeshkaram M Thyroid autoimmunity in pregnancy and its influences on maternal and fetal outcome in Iran (a prospective study). Endocrine research. 40:139–145; 2015 [PubMed: 25330412]

Shah-Kulkarni S; Kim BM; Hong YC; Kim HS; Kwon EJ; Park H; Kim YJ; Ha EH Prenatal exposure to perfluorinated compounds affects thyroid hormone levels in newborn girls. Environ Int. 94:607–613; 2016 [PubMed: 27395336]

Shields BM; Knight BA; Hill A; Hattersley AT; Vaidya B Fetal thyroid hormone level at birth is associated with fetal growth. J Clin Endocrinol Metab. 96:E934–938; 2011 [PubMed: 21411545]

Sonthithai P; Suriyo T; Thiantanawat A; Watcharasit P; Ruchirawat M; Satayavivad J Perfluorinated chemicals, PFOS and PFOA, enhance the estrogenic effects of 17β-estradiol in T47D human breast cancer cells. Journal of Applied Toxicology. 36:790–801; 2016 [PubMed: 26234195]

Stoffer SS Williams Textbook of Endocrinology: Saunders/Elsevier; 2008

Thibodeaux JR; Hanson RG; Rogers JM; Grey BE; Barbee BD; Richards JH; Butenhoff JL; Stevenson LA; Lau C Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. I: maternal and prenatal evaluations. Toxicological sciences : an official journal of the Society of Toxicology. 74:369–381; 2003 [PubMed: 12773773]

Tsai MS; Lin CC; Chen MH; Hsieh WS; Chen PC Perfluoroalkyl substances and thyroid hormones in cord blood. Environmental pollution (Barking, Essex : 1987). 222:543–548; 2017

Wang B; Chen Q; Shen L; Zhao S; Pang W; Zhang J Perfluoroalkyl and polyfluoroalkyl substances in cord blood of newborns in Shanghai, China: Implications for risk assessment. Environ Int. 97:7–14; 2016 [PubMed: 27770709]

Wang X; Ouyang F; Feng L; Wang X; Liu Z; Zhang J Maternal Urinary Triclosan Concentration in Relation to Maternal and Neonatal Thyroid Hormone Levels: A Prospective Study. Environmental health perspectives. 125:067017; 2017 [PubMed: 28669941]

Wang Z; Cousins IT; Scheringer M; Buck RC; Hungerbuhler K Global emission inventories for C4-C14 perfluoroalkyl carboxylic acid (PFCA) homologues from 1951 to 2030, part II: the remaining pieces of the puzzle. Environ Int. 69:166–176; 2014 [PubMed: 24861268]

Weiss JM; Andersson PL; Lamoree MH; Leonards PE; van Leeuwen SP; Hamers T Competitive binding of poly- and perfluorinated compounds to the thyroid hormone transport protein transthyretin. Toxicological sciences : an official journal of the Society of Toxicology. 109:206–216; 2009 [PubMed: 19293372]

Xing G; Lin CY; Xing C A comparison of approaches to control for confounding factors by regression models. Human heredity. 72:194–205; 2011 [PubMed: 22086357]

Yang L; Li J; Lai J; Luan H; Cai Z; Wang Y; Zhao Y; Wu Y Placental Transfer of Perfluoroalkyl Substances and Associations with Thyroid Hormones: Beijing Prenatal Exposure Study. Sci Rep. 6:21699; 2016 [PubMed: 26898235]

Yu WG; Liu W; Jin YH Effects of perfluorooctane sulfonate on rat thyroid hormone biosynthesis and metabolism. Environmental toxicology and chemistry. 28:990–996; 2009 [PubMed: 19045937]

Table 1.

Maternal and fetal characteristics* (N=568)

Characteristics	N	Mean ± SD or n (%)
Mother		
Maternal age (years)	568	29.6 ± 4.4
Pre-pregnancy body mass index	566	21.8 ± 3.7
Parity		
Nulliparous	506	89.1
Parous	62	10.9
Maternal alcohol intake		
Yes	11	1.9
No	557	98.1
Maternal education		
High School or lower	64	11.3
College	465	82.0
Master's degree or above	38	6.7
Gestational age at delivery (weeks)	568	38.8 ± 0.9
Fish consumption		
≤ 1-2 times/month	229	40.3
≥ 1-2 times/week	339	59.7
Fetus		
Birth weight (g)	568	3450 ± 433.5
Birth length (cm)	565	49.9 ± 1.3
Gender		
Male	305	53.8
Female	262	46.2

*The missing data: Pre-pregnancy body mass index (n=2); maternal education (n=1); Birth length (n=3); gender (n=1)

Table 2.

Distribution of PFAS and thyroid hormone levels in umbilical cord blood (N= 568) *

Items	% > LOD	GM	Range	Percentiles			
				P25	P50	P75	P95
PFAS [a] (ng/mL)							
PFOA	100	7.57	1.61 - 33.94	5.65	7.57	9.98	14.75
PFOS	100	2.53	0.39 - 65.61	1.85	2.51	3.34	5.50
PFNA	100	0.67	0.11 - 9.16	0.52	0.66	0.85	1.24
PFDA	99.6	0.39	< LOD - 20.54	0.27	0.41	0.57	1.06
PFUA	99.8	0.41	< LOD - 22.41	0.31	0.40	0.54	0.91
PFHxS	100	0.19	0.08 - 1.00	0.14	0.18	0.25	0.36
PFDoA	93.1	0.11	< LOD - 2.22	0.08	0.11	0.17	0.25
PFBS	98.4	0.06	< LOD - 0.46	0.04	0.05	0.09	0.14
PFHpA	46.0	< LOD	< LOD - 0.82	< LOD	< LOD	0.10	0.20
PFOSA	19.5	< LOD	< LOD - 0.18	< LOD	< LOD	< LOD	0.13
Thyroid hormones							
FT3 [b] (pmol/L)	82.4	1.89	< LOD - 4.29	1.69	2.03	2.34	2.75
FT4 [c] (pmol/L)	99.8	13.54	< LOD - 18.44	12.74	13.48	14.39	15.93
TSH (mIU/L)	100	4.79	1.73 - 28.87	3.76	4.66	5.85	9.14

* FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; GM: geometric mean; P25 ~ P95:25th ~ 95th percentiles. Missing data: FT3 (n=4); TSH (n=1)

[a] PFAS limit of detection (LOD, ng/mL): PFOA (0.09), PFOS (0.09), PFNA (0.02), PFDA (0.02), PFUA (0.02), PFHxS (0.02), PFDoA (0.05), PFBS (0.009), PFOSA (0.12), PFHpA (0.03).

[b] FT3 LOD= 1.54 pmol/L.

[c] FT4 LOD= 5.15pmol/L.

Table 3.

Estimates of association between PFAS and thyroid hormones in cord blood among prelabor cesarean deliveries by sparse partial least square (SPLS)[a] (N=568)

Exposure[b]	FT4 β (95%CI)	FT3 β (95%CI)	TSH β (95%CI)
All[c]	**η= 0.99, K= 1**	**η= 0.67, k =2**	**η= 0.67, k =1**
PFOA	—	—	—
PFOS	—	0.059 (0.023, 0.100)	−0.012 (−0.019, −0.005)
PFNA	—	0.024 (−0.027, 0.071)	−0.012 (−0.019, −0.005)
PFDA	—	−0.008 (−0.04, 0.026)	−0.012 (−0.02, −0.005)
PFUA	—	0.018 (−0.034, 0.077)	−0.013 (−0.021, −0.006)
PFHxS	—	—	—
PFDoA	0.190 (0.063, 0.304)	−0.153 (−0.212, −0.106)	−0.013 (−0.023, −0.006)
PFBS	—	—	—
Boy[d]	**η= 0.15, k =1**	**η= 0.93, k =5**	**η= 0.99, k =2**
PFOA	0.062 (0.024, 0.138)	−0.068 (−0.151, 0.015)	—
PFOS	0.023 (−0.035, 0.057)	0.034 (−0.069, 0.185)	—
PFNA	0.040 (0.006, 0.081)	0.075 (−0.07, 0.216)	—
PFDA	0.043 (0.016, 0.078)	—	—
PFUA	0.033 (−0.007, 0.069)	0.107 (−0.069, 0.234)	—
PFHxS	0.024 (−0.024, 0.067)	—	—
PFDoA	0.054 (0.019, 0.119)	−0.251 (−0.361, −0.144)	−0.062 (−0.108, −0.017)
PFBS	0.056 (0.009, 0.158)	0.098 (0.021, 0.182)	−0.047 (−0.103, 0.011)
Girl[d]	**η= 0.99, k =1**	**η= 0.99, k =1**	**η= 0.61, k =1**
PFOA	—	—	—
PFOS	—	—	−0.016 (−0.032, −0.002)
PFNA	—	—	−0.015 (−0.031, 0.001)
PFDA	—	—	−0.013 (−0.026, 0.01)
PFUA	—	—	−0.018 (−0.033, 0.003)
PFHxS	—	—	—
PFDoA	0.174 (0.019, 0.331)	−0.124 (−0.185, −0.056)	—
PFBS	—	—	0.011 (−0.003, 0.059)

[a]Regression coefficients (β) and 95% confidence intervals calculated using SPLS models; —, indicates association was not selected in SPLS model; SPLS tuning parameters: k: the number of components used to construct the model, η: the degree of sparsity; the 95% CI of coefficients was obtained via bootstrapping with 1000 iterations.

[b]All natural log-transformed PFAS were standardized, TSH was natural log-transformed. The regression coefficients (β) and 95%CIs were presented as changes in THs level per unit increase in PFAS

[c]Models adjusting for maternal age, fish intake, parity, infant sex, gestational age at delivery and maternal pre-pregnancy BMI

[d]Models adjusting for maternal age, fish intake, parity, gestational age at delivery and maternal pre-pregnancy BMI