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Association between perfluoroalkyl substance exposure and thyroid hormone/thyroid antibody levels in maternal and cord blood: The Hokkaido Study

Sachiko Itoh[a], Atsuko Araki[a], Chihiro Miyashita[a], Keiko Yamazaki[a], Houman Goudarzi[a,b], Machiko Minatoya[a,c], Yu Ait Bamai[a], Sumitaka Kobayashi[a], Emiko Okada[d], Ikuko Kashino[d], Motoyuki Yuasa[e], Toshiaki Baba[a,f], Reiko Kishi[a,*]

[a] Center for Environmental Health and Sciences, Hokkaido University, Sapporo, Japan
[b] Department of Respiratory Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan
[c] Faculty of Health Sciences, Hokkaido University, Sapporo, Japan
[d] Department of Public Health, Hokkaido University Graduate School of Medicine, Sapporo, Japan
[e] Department of Public Health, School of Medicine, Juntendo University, Japan
[f] National Center for Global Health and Medicine, Japan

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ABSTRACT

Background: Thyroid antibodies (TAs) are the most common cause of hypothyroidism during gestation. Although previous studies found that prenatal exposure to perfluoroalkyl substances (PFASs) disrupts thyroid hormones (THs) in humans, their effects on TAs during the perinatal period have not been investigated.

Objective: To explore the associations between prenatal exposure to eleven different PFASs from two different groups (carboxylates and sulfonates) and the expression of THs and TAs in maternal and cord blood while considering maternal TA status.

Methods: In a prospective birth cohort (the Hokkaido Study), we included 701 mother-neonate pairs recruited in 2002–2005 for whom both prenatal maternal and cord blood samples were available. Eleven PFASs were measured in maternal plasma obtained at 28–32 weeks of gestation using ultra-performance liquid chromatography coupled with triple quadrupole tandem mass spectrometry. THs and TAs including thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TgAb) were measured in maternal blood during early pregnancy (median 11 gestational weeks), and in cord blood at birth.

Results: The median levels of TgAb and TPOAb in maternal serum were 15.0 and 6.0 IU/mL, respectively. The median TgAb level in neonates was 38.0 IU/mL, and TPOAb were detected in only 12.3% of samples. Maternal FT3 level was positively associated with PFAS levels in both TA-positive and TA-negative mothers. Maternal perfluorooctanoate was inversely associated with maternal TPOAb. Among boys, some maternal PFASs were associated with higher TSH and lower FT3 levels in maternal TA-negative group, while perfluorodecanoic acid was associated with lower TSH in maternal TA-positive group. Among girls, some PFAS of mothers showed associations with lower TSH and higher FT3 in maternal TA-negative group, while perfluorododecanoic acid was associated with lower FT4 in maternal TA-positive. Maternal PFASs showed associations with boy's TgAb inversely in maternal TA-negative group and with girl's TgAb positively in maternal TA-positive group.

Conclusions: Our results suggest thyroid disrupting effects of PFAS exposure and susceptibility vary depending on maternal TA levels.

Abbreviations: FT3, free triiodothyronine; FT4, free thyroxine; PFASs, perfluoroalkyl substances; PFDA, perfluorodecanoic acid; PFDoDA, perfluorododecanoic acid; PFHpA, perfluoroheptanoic acid; PFHxA, perfluorohexanoic acid; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoate; PFTeDA, perfluorotetradecanoic acid; PFTrDA, perfluorotridecanoic acid; PFUnDA, perfluoroundecanoic acid; TgAb, thyroid peroxidase antibody; TPOAb, thyroglobulin antibody; TSH, thyroid-stimulating hormone

* Corresponding author at: Center for Environmental Health and Sciences, Hokkaido University, North 12 West 7, Kita-ku, Sapporo 060-0812, Japan.
E-mail address: rkishi@med.hokudai.ac.jp (R. Kishi).

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1. Introduction

Perfluoroalkyl substances (PFASs) are widely-used in industrial products and are commonly detected in the environment. Human exposure to PFASs mainly occurs via the intake of contaminated food, water, and dust (Fromme et al., 2009). Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) are the most commonly detected PFASs in the environment and in humans, and their presence in human blood has been reported in several countries (Butenhoff et al., 2006; Calafat et al., 2007; Harada et al., 2007; Midasch et al., 2007). Furthermore, PFOS was added to Annex B of the Stockholm Convention on Persistent Organic Pollutants in 2009, while PFOA is now also under consideration for listing in the Stockholm Convention by the European Union. Although PFOS and PFOA are being voluntarily phased out by several industries, they are still present in older products and have long half-lives in human serum (PFOS: 5.3 years; PFOA: 3.8 years) (Olsen et al., 2007). Recently, other PFASs that replaced PFOS and PFOA, such as perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA), have emerged (Okada et al., 2013). PFASs can cross the placental barrier and transfer from human mothers to fetuses (Gutzkow et al., 2012; Inoue et al., 2004; Midasch et al., 2007). Therefore, significant concern has been raised regarding the adverse effects of in utero exposure of fetuses to PFASs.

Epidemiological studies have found that prenatal exposure to PFASs is inversely associated with birth size and neurodevelopment during childhood (Apelberg et al., 2007; Chen et al., 2013). Our group, the Hokkaido Study on the Environment and Children's Health, also reported an inverse association between maternal PFOS serum levels and birth weight among female neonates and neurodevelopment in early infancy (Goudarzi et al., 2016b; Washino et al., 2009). Moreover, we found significant associations between exposure to PFOS and reduced essential fatty acid and triglyceride serum levels in pregnant mothers (Kishi et al., 2015) as well as altered reproductive and steroid hormone levels (Goudarzi et al., 2017a; Itoh et al., 2016). Moreover,The levels of PFOS and PFOA were lower than those found in other countries and in other areas of Japan (Okada et al., 2013).

Thyroid hormones (THs) are critical for neurodevelopmental growth during gestation and are also essential for behavioral and cognitive functions during infancy and childhood. Fetuses depend on their mothers' supply of TH in early gestation; hence, even mild maternal hypothyroxinemia during pregnancy increases the risk of adverse effects on fetal neurodevelopment (Haddow et al., 1999). Recent studies have suggested that PFASs may impair the levels of THs owing to their competitive binding to TH transporters (Weiss et al., 2009). Previous prospective studies in human patients concluded that prenatal exposure to PFASs alters the balance of THs in infants (de Cock et al., 2014; Kim et al., 2011; Shah-Kulkarni et al., 2016; Tsai et al., 2017). Our previous study also revealed a significant association between maternal PFOS levels during pregnancy and decreased maternal thyroid-stimulation hormone (TSH) as well as increased infant TSH (Kato et al., 2016). Recently, a small study in Canada found that PFAS exposure was associated with increased maternal TSH among women with high thyroid peroxidase antibody (TPOAb) (Webster et al., 2014), while Project Viva in the United States showed that PFASs were inversely associated with TSH levels in TPOAb-positive women (Preston et al., 2018; Reardon et al., 2019). Those three studies indicated that TPOAb might be the effect modifier of the associations between PFASs and THs.

Thyroid antibodies (TAs) are also worthy of attention. Since TPOAb and thyroglobulin antibody (TgAb) inhibit initial TH biosynthesis, TH levels are affected by TA levels (Balucan et al., 2013). In routine clinical settings, TPOAb and TgAb are measured to identify antibody-positive patients based on a cut-off value. Williams et al. (2013) reported that 16% and 31% of women were identified as TPOAb- and/or TgAb- positive, respectively, at 10 weeks of gestation. High levels of TAs have been linked to increased risks of immune-mediated miscarriages and postpartum thyroiditis. A previous experimental study revealed that PFAS decreased thyroid peroxidase (TPO) activity in cells (Song et al., 2012); therefore, it is also posited that autoimmune damage by PFASs to the thyroid could render individuals more susceptible to the thyroid-altering effects of PFASs, leading to decreased TH synthesis (Balucan et al., 2013). Only one cross-sectional study reported a positive association between perfluorohexanoic acid (PFHxA) and TgAb serum levels in 202 Chinese individuals aged between 1 month and 91 years (Li et al., 2017). However, no studies have been conducted exploring the association between PFAS exposure and TA levels during perinatal period, as even subtle changes in the values of the latter during pregnancy might cause thyroid diseases or dysregulate thyroid hormone production (Matarese et al., 2003). Moreover, there are no studies on this matter in neonates, even though TPOAb and/or TgAb in mothers are assumed to be transferred to their fetuses (Pop et al., 1995).

Therefore, we aimed to investigate the effects of prenatal exposure to PFASs on both maternal and neonatal THs as well as TPOAb and TgAb using data from a prospective birth cohort study. We also explored modification effects of maternal TPOAb and TgAb levels in the associations between PFASs and THs or TA levels. This is the first study to date to explore TA levels in healthy mothers and infants in an analysis of PFAS exposure and thyroid status.

2. Materials and methods

2.1. Participants

This prospective birth cohort was based on the Hokkaido Study on the Environment and Children's Health. Details regarding the study population, data collection, biological specimen sampling, and questionnaire contents have been described previously (Kishi et al., 2011; Kishi et al., 2013; Kishi et al., 2017). In brief, native Japanese citizens who received antenatal health care during early pregnancy (> 13 weeks of gestational age) at any of the 37 hospitals and clinics in Hokkaido Prefecture participating in this study were eligible. Among 20,926 mother-child pairs registered in the Hokkaido Study between 2003 and 2011, we randomly selected 1000 from 1188 mother-child pairs who met the following criteria: children born between 2003 and 2005, submitted to a baseline questionnaire, and had both maternal blood at early gestational stage and cord blood available. There were 117 pairs excluded owing to insufficient blood samples for measuring TH levels, as well as 182 pairs excluded for having no PFAS data. Totally, 701 mother-neonate pairs were included in the study of the associations between maternal PFASs and maternal or neonatal TH levels. Among 701 pairs, 499 pairs also had the data of maternal TAs, meanwhile, 202 mothers did not have the data of TAs because of the lack of sample blood volume. Therefore, we analyzed the relationships between maternal PFASs and maternal or neonatal TA levels, and explored the modification effect of maternal TAs in 499 pairs with the data of maternal TAs. This study was conducted in accordance with the Declaration of Helsinki; the protocol was approved by the institutional ethical board for epidemiological studies at the Hokkaido University Graduate School of Medicine and Hokkaido University Center for Environment and Health Sciences. Written informed consent was obtained from all participants.

2.2. Exposure assessment

Detailed sample preparation and PFAS measurement methods were previously described (Okada et al., 2013; Goudarzi et al., 2017b). Maternal peripheral vein blood samples were collected and stored at −80 °C until analysis. We used maternal plasma for exposure assessment using ultra-performance liquid chromatography coupled with triple quadrupole tandem mass spectrometry instrumentation (Waters, Milford, MA, USA). We measured the concentrations of two groups of PFASs: perfluoroalkane sulfonates, including perfluorohexane sulfonate (PFHxS) and PFOS; and perfluorinated carboxylic acids including

PFHxA, perfluoroheptanoic acid (PFHpA), PFOA, PFNA, PFDA, perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorotridecanoic acid (PFTrDA), and perfluorotetradecanoic acid (PFTeDA) for a total of 11 PFASs in maternal plasma samples obtained between 28 and 32 weeks of pregnancy. The method detection limits (MDLs) were 0.1 ng/mL for PFHxA, PFHpA, PFDA, PFUnDA, PFDoDA, PFTrDA, and PFTeDA; 0.2 ng/mL for PFHxS and PFOA; and 0.3 ng/mL for PFOS and PFNA. Samples with PFAS levels below the detection limit were assigned a value of half the detection limit.

2.3. Outcome measures

Blood samples (10–30 mL) were collected from each mother during pregnancy (mean and standard deviation; 11.35 and 3.5, median (range); 11(9–13) of gestational weeks) as well as from the umbilical cords at the time of delivery; these were stored at −80 °C until the time of analysis. We used maternal and cord blood serum samples for TH levels (TSH, FT3, and FT4), and for TA levels (TPOAb and TgAb) using an electrochemiluminescence immunoassay. Using laboratory standards, TPOAb-positivity was considered ≥16 IU/mL, while TgAb-positivity was considered ≥28 IU/mL. All thyroid parameter measurements were performed at SRL Inc. (Tokyo, Japan). The MDLs were 0.005 μU/mL for TSH, 0.26 pg/mL for FT3, 0.3 pg/mL for FT4, 5.0 IU/mL for TPOAb, and 10.0 IU/mL for TgAb. Samples that expressed levels below the test LODs were assigned values of half the LOD.

2.4. Questionnaire and medical records

All participants completed a self-administered questionnaire at enrollment regarding their maternal age, educational level, annual household income, alcohol consumption, smoking status, and medical history. Maternal smoking status during pregnancy was classified as nonsmoker (never smoked or stopped smoking during the first trimester) versus smoker (had smoked after the first trimester). Maternal alcohol consumption during pregnancy was classified as nondrinker (never drank alcohol or stopped drinking during the first trimester) versus drinker (had drank alcohol after the first trimester). Medical records were obtained to collect information regarding body mass index (BMI) before pregnancy, pregnancy complications, gestational age, child sex, parity, and neonatal birth sizes.

2.5. Statistical analyses

Analyses of the associations between maternal PFAS levels and maternal thyroid status during pregnancy were designed as a cross-sectional study, while the analyses of the associations between maternal PFAS levels and neonatal thyroid statuses at birth were designed as a prospective study. Total PFAS levels were calculated as the sum of each PFAS (ng/mL), using values of half the detection limit under LODs. The correlations between PFAS and the maternal and neonate characteristics were explored using Spearman's correlation test and the Mann-Whitney *U* test. Correlations of maternal serum PFAS levels with maternal and cord blood TH levels were analyzed using Spearman's correlation test. In multiple regression analysis, both maternal and neonatal analysis, participants were stratified by maternal TA status (positive/negative of maternal TPOAb and/or TgAb). On linear regression analysis, levels of PFAS and THs were converted to a natural log scale to account for their skewed distributions. We constructed directed acyclic graphs to determine potential confounders in the fully adjusted model; the set of variables used in these graphs were selected from information in previous publications. For maternal thyroid status analysis, values were adjusted for maternal age at delivery (years), parity (0/≥1), educational level (years: < 13/≥13), pre-pregnancy BMI (kg/m^2) (continuous values), alcohol intake during pregnancy (yes/no) and smoking during pregnancy (yes/no). For neonate TH and TgAb analysis, we selected maternal age at delivery (years), parity (0/≥1), educational level (years: < 13/≥13), pre-pregnancy BMI (kg/m^2) (continuous values), alcohol intake during pregnancy (yes/no), smoking during pregnancy (yes/no), and logFT4 (continuous values), stratifying by sex. All statistical analyses were performed using JMP Pro software (version 14; SAS Institute Inc., NC, USA).

Table 1
Characteristics of mothers and neonates included in this study (n = 701).

Characteristics		n (%)	Mean ± SD
Maternal characteristics			
Age at delivery (years)		701	30.7 ± 4.4
Pre-pregnancy body mass index (kg/m^2)		694	21.0 ± 2.9
Parity	Primiparous	307 (43.8)	
	Multiparous	390(55.6)	
Annual household income (million yen per year)	< 5	374 (53.3)	
	≥5	236(33.7)	
Educational level (years)	≤12	285(40.7)	
	≥13	410 (58.5)	
Smoking during pregnancy	Nonsmoker	549(78.3)	
	Smoker	52 (7.4)	
Alcohol consumption during pregnancy	Nondrinker	359 (51.2)	
	Drinker	112 (16.0)	
Neonatal characteristics			
Sex	Boys	365 (52.1)	
	Girls	336 (47.9)	
Birth weight (g)		701	3063.6 ± 360.6
Gestational weeks for birth		701	38.9 ± 1.2

SD: standard deviation.

3. Results

Among 701 mother-child pairs, the average maternal age at birth (± standard deviation) was 30.7 ± 4.4 with an average pre-pregnancy BMI of 21.0 + 2.9 kg/m^2. Furthermore, 55.6% of mothers were multiparous, and the maternal smoking and alcohol consumption rate during pregnancy were 7.4% and 16.0, respectively. A total of 51.2% of children were male (Table 1). There was no significant difference in characteristics between TA positive group and negative group. Table 2 shows the maternal plasma levels of 11 PFAS. The detection rates of the six PFAS were higher than 96%; PFOS was predominant with 6.21 ng/mL (interquartile range [IQR]: 4.70–8.30 ng/mL), followed by PFOA with 2.00 ng/mL (IQR: 1.41–2.83 ng/mL), and PFUnDA with 1.34 ng/mL (IQR: 0.84–1.80 ng/mL). Because of their low detection rates (< 40%), PFHxA, PFHpA, and PFTeDA levels were excluded from linear regression analysis models.

The distributions of TH and TA levels are shown in Table 3. TH levels were measured in all samples from mothers and neonates, while TPOAb and TgAb were measured in 499 and 693 samples from mothers and neonates, respectively, owing to insufficient blood samples. Maternal TSH and TgAb levels were much lower than those of neonates, while maternal FT3 levels were higher than neonatal counterparts. Maternal FT3 and FT4 were detected in all samples; maternal TSH levels were above the LOD in 686 samples (97.9%). TPOAb was detected in 67.3% of maternal samples. Forty-five women were TPOAb-positive (9.0%), while 79 were TgAb-positive (15.8%). Among neonates, TSH, FT3, FT4, and TgAb were detected in all cord blood samples, while TPOAb was detected only in 12.3%; therefore, we excluded neonatal TPOAb from further analysis. Furthermore, 474 neonates were TgAb-positive (95.0%). Supplemental Table 1 shows the correlations between maternal and neonatal thyroid status; neonatal FT4 level was significantly correlated with maternal THs. Neonatal TgAb was also moderately correlated with maternal TSH, and maternal TPOAb was correlated with neonatal TSH.

Supplemental Tables 2 and 3 show the relationships between maternal PFAS and TH and TA levels, and we selected significant associations in Table 4. As for TH, analysis was also conducted stratifying by

Table 2
Concentrations of PFAS levels (ng/mL) in maternal serum (n = 701).

	MDL	No. with > LOD	Detection rate (%)	Minimum	25th	50th	75th	Maximum
PFHxA (C6)	0.1	246	35.1	< 0.1	< 0.1	< 0.1	0.13	0.48
PFHxS (C6)	0.2	572	81.6	< 0.2	0.22	0.31	0.42	1.77
PFHpA (C7)	0.1	232	33.1	< 0.1	< 0.1	< 0.1	0.11	0.62
PFOS (C8)	0.3	701	100.0	1.15	4.70	6.21	8.30	30.28
PFOA (C8)	0.2	699	99.7	< 0.2	1.41	2.00	2.83	12.37
PFNA (C9)	0.3	697	99.4	< 0.3	0.78	1.01	1.38	6.64
PFDA (C10)	0.1	694	99.0	< 0.1	0.35	0.49	0.65	1.59
PFUnDA (C11)	0.1	698	99.6	< 0.1	0.84	1.34	1.80	5.89
PFDoDA (C12)	0.1	613	87.4	< 0.1	0.12	0.16	0.22	0.65
PFTrDA (C13)	0.1	673	96.0	< 0.1	0.24	0.33	0.44	1.33
PFTeDA (C14)	0.1	50	7.1	< 0.1	< 0.1	< 0.1	< 0.1	0.24
Total PFAS	–	–	–	3.07	9.96	12.46	15.90	42.67

Total PFAS were calculated as the sum of each PFAS. PFAS: perfluoroalkyl substance, MDL: method detection limit, LOD: limit of detection, PFHxA: perfluorohexanoic acid, PFHxS: perfluorohexane sulfonate, PFHpA: perfluoroheptanoic acid, PFOS: perfluorooctane sulfonate, PFOA: perfluorooctanoate, PFNA: perfluorononanoic acid, PFDA: perfluorodecanoic acid, PFUnDA: perfluoroundecanoic acid, PFDoDA: perfluorododecanoic acid, PFTrDA: perfluorotridecanoic acid, PFTeDA: perfluorotetradecanoic acid.

maternal TA status (TPOAb and/or TgAb positive or negative). After fully adjusting for potential confounders, maternal PFHxS showed significant positive association with FT3 level among TA-negative group (β = 0.043, 95% confidence interval [CI]: 0.003, 0.083, p = 0.037). In maternal TA-positive group, maternal PFNA was significantly associated with FT3 level positively (β = 0.180, 95% CI: 0.013, 0.347, p = 0.035). TSH and FT4 levels were not associated with any PFAS in both groups. Maternal PFOA levels exhibited a significant inverse association with maternal TPOAb (β = −0.228, 95% CI: −0.439, −0.018, p = 0.033). The relationships between maternal PFAS and neonatal TH and TgAb levels were shown in Supplemental Tables 4–9. We selected significant associations in Table 5 (boys) and Table 6 (girls). Table 5 shows that maternal PFOS positively associated with boy's TSH among all boys (β = 0.230, 95% CI: 0.074, 0.385, p = 0.004). In boys whose mothers were maternal TA-negative, maternal PFOS was found to be significantly associated with higher TSH levels (β = 0.389, 95% CI: 0.122, 0.656, p = 0.005), while PFDA and PFUnDA showed significant inverse association with FT3 (β = −0.186, 95% CI: −0.366, −0.006, p = 0.043, β = −0.172, 95% CI: −0.329, −0.014, p = 0.033, respectively). As for TgAb, PFOA and PFTrDA were significantly associated with lower TgAb levels (β = −0.134, 95% CI: −0.266, −0.002, p = 0.047, β = −0.119, 95% CI: −0.226, −0.013, p = 0.028, respectively). We also found significant interaction effects between maternal PFTrDA and maternal TA-status (positive or negative) for boy's TgAb (p-interaction = 0.008). Among maternal TA-positive group, maternal PFDA was significantly associated with lower boy's TSH (β = −1.036, 95% CI: −1.644, −0.428, p = 0.004). There were no significant association between maternal PFASs and boy's TgAb in maternal TA-positive group. FT4 was not influenced by maternal PFAS exposure in any group. Table 6 shows that maternal PFDoDA showed significant inverse association with TSH in girls whose mothers with TA-negative (β = −0.181, 95% CI: −0.345, −0.018, p = 0.030). PFDA and PFTrDA were significantly associated with higher FT3 (β = 0.258, 95% CI: 0.057, 0.460, p = 0.013, β = 0.226, 95% CI: 0.070, 0.382, p = 0.005, respectively). Furthermore, we found significant interaction effects between maternal PFTrDA and maternal TA status (positive or negative) (p-interaction = 0.031) for girl's FT3. In mothers with TA-positive group, maternal PFDoDA showed significant inverse association with girl's FT4 level (β = −0.077, 95% CI: −0.148, −0.006, p = 0.037). We also found significant positive associations between PFOA, PFNA, PFDA and Total PFAS and girl's TgAb (β = 0.266, 95% CI: 0.095, 0.437, p = 0.007, β = 0.284, 95% CI: 0.070, 0.498, p = 0.015, β = 0.267, 95% CI: 0.145, 0.389, p ≤ 0.001, β = 0.495, 95% CI: 0.205, 0.786, p = 0.0054, respectively). On the other hand, we found no significant association before stratifying by maternal TA status.

4. Discussion

We found that maternal PFAS exposure at environmental levels during pregnancy is significantly associated with not only maternal and neonatal THs and but also TA levels. To our knowledge, this study is the first to investigate the effects of prenatal PFAS exposure on TAs among mother-neonate pairs. Moreover, our result indicated that maternal TA status might be one of the effect modifier in the relationships between PFASs and neonatal THs and TgAb.

Previous studies that evaluated the associations between maternal PFAS exposure and maternal and/or neonatal TH levels exist. In terms

Table 3
Distribution of thyroid hormone and antibody levels in mothers and neonates (n = 701).

	MDL	No. with > LOD	Detection rate (%)	Minimum	25th	50th	75th	Maximum
Mothers								
TSH (μU/mL)	0.005	686	97.9	< 0.005	0.323	0.802	1.400	157.500
FT3 (pg/mL)	0.26	701	100	1.28	2.78	3.04	3.38	8.75
FT4 (pg/mL)	0.3	701	100	7.4	12.1	13.5	15.1	44.4
TPOAb (IU/mL)	5.0	336	67.3	< 5.0	< 5.0	6.0	8.0	600.0
TgAb (IU/mL)	10.0	455	91.2	< 10.0	12.0	15.0	20.0	382.5
Neonates								
TSH (μU/mL)	0.005	701	100	1.76	5.74	7.98	12.00	79.27
FT3 (pg/mL)	0.26	661	94.3	< 0.26	1.14	1.29	1.45	5.19
FT4 (pg/mL)	0.3	701	100	9.3	1.2012.0	13.0	14.3	47.2
TPOAb (IU/mL)	5.0	85	12.3	< 5.0	< 5.0	< 5.0	< 5.0	600.0
TgAb (IU/mL)	10.0	693	100	18.0	33.0	38.0	45.0	886.0

MDL: method detection limit, LOD: limit of detection, TSH: thyroid-stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, TPOAb: thyroglobulin antibody, TgAb: thyroid peroxidase antibody.

Table 4
Linear regression models of maternal PFAS levels and thyroid hormone and antibody levels among mothers (n = 701 or 499).

	PFASs	All mothers (n = 701 or 499)		TA negative (n = 406)		TA positive (n = 493)		p-interaction
		B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value	
FT3	PFHxS (C6)	N.S.		0.043 (0.003, 0.083)	0.037	N.S.		N.S.
	PFNA (C9)	N.S.		N.S.		0.180 (0.013, 0.347)	0.035	N.S.
TPOAb	PFOA (C8)	−0.228 (−0.439, −0.018)	0.033					N.S.

All mothers included 701 mothers for the analysis of the associations between PFASs and thyroid hormones (TSH, FT3, FT4), while 499 mothers for the analysis of the associations between PFASs and thyroid antibodies (TPOAb and TgAb). Adjusted for age at delivery, parity, pre-pregnancy BMI, educational level, alcohol consumption and smoking habit during pregnancy. *p < 0.05, **p < 0.01.
"N.S." means not significant association, and blank cell means not analyzed in this study.
PFAS: perfluoroalkyl substance, TA: thyroid antibody, TSH: thyroid-stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, TgAb: thyroid peroxidase antibody, TPOAb: thyroglobulin antibody, PFHxS: perfluorohexane sulfonate, PFNA: perfluorononanoic acid, and PFOA: perfluorooctanoate.

Table 5
Linear regression models of maternal PFAS levels and thyroid hormone and TgAb levels among boys (n = 365 or 259).

	PFASs	All boys (n = 365 or 259)		Maternal TA negative (n = 211)		Maternal TA positive (n = 48)		p-interaction
		B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value	
TSH[a]	PFOS (C8)	0.230 (0.074, 0.385)	0.004	0.389 (0.122, 0.656)	0.005	N.S.		N.S.
	PFDA (C10)	N.S.		N.S.		−1.036 (−1.644, −0.428)	0.004	N.S.
FT3[a]	PFDA (C10)	N.S.		−0.186 (−0.366, −0.006)	0.043	N.S.		N.S.
	PFUnDA(C11)	N.S.		−0.172 (−0.329, −0.014)	0.033	N.S.		N.S.
TgAb[b]	PFOA (C8)	N.S.		−0.134 (−0.266, −0.002)	0.047	N.S.		N.S.
	PFTrDA (C13)	N.S.		−0.119 (−0.226, −0.013)	0.028	N.S.		0.008

"All boys" included 365 boys for the analysis of the associations between maternal PFASs and thyroid hormones (TSH, FT3, FT4), while 259 boys for the analysis of the associations between maternal PFASs and TgAb. "N.S." means not significant association. *p < 0.05, **p < 0.01.
PFAS: perfluoroalkyl substance, TA: thyroid antibody, TSH: thyroid-stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, TgAb: thyroid peroxidase antibody, PFOS: perfluorooctane sulfonate, PFOA: perfluorooctanoate, PFDA: perfluorodecanoic acid, PFUnDA: perfluoroundecanoic acid, PFTrDA: perfluorotridecanoic acid.
[a] Adjusted for maternal factors (age at delivery, parity, educational level, alcohol consumption, smoking during pregnancy, pre-pregnancy BMI, logFT4).
[b] Adjusted for maternal factors (age at delivery, parity, educational level, alcohol consumption, smoking during pregnancy, pre-pregnancy BMI).

Table 6
Linear regression models of maternal PFAS levels and thyroid hormone and TgAb levels among girls (n = 336 or 240).

	PFASs	All girls (n = 336 or 240)		Maternal TA negative (n = 195)		Maternal TA positive (n = 45)		p-interaction
		B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value	
TSH[a]	PFDoDA(C12)	N.S.		**−0.181 (−0.345, −0.018)**	**0.030**	N.S.		N.S.
FT3[a]	PFDA (C10)	N.S.		**0.258 (0.057, 0.460)**	**0.013**	N.S.		N.S.
	PFTrDA (C13)	N.S.		**0.226 (0.070, 0.382)**	**0.005**	N.S.		**0.031**
FT4[a]	PFDoDA(C12)	N.S.		N.S.		**−0.077 (−0.148, −0.006)**	**0.037**	N.S.
TgAb[b]	PFOA (C8)	N.S.		N.S.		**0.266 (0.095, 0.437)**	**0.007**	N.S.
	PFNA (C9)	N.S.		N.S.		**0.284 (0.070, 0.498)**	**0.015**	N.S.
	PFDA (C10)	N.S.		N.S.		**0.267 (0.145, 0.389)**	**< 0.001**	N.S.
	Total PFASs	N.S.		N.S.		**0.495 (0.205, 0.786)**	**0.004**	N.S.

"All girls" included 336 girls for the analysis of the associations between maternal PFASs and thyroid hormones (TSH, FT3, FT4), while 240 girls for the analysis of the associations between maternal PFASs and TgAb. "N.S." means not significant association. *p < 0.05, **p < 0.01.
PFAS: perfluoroalkyl substance, TA: thyroid antibody, TSH: thyroid-stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, TgAb: thyroid peroxidase antibody, PFOA: perfluorooctanoate, PFNA: perfluorononanoic acid, PFDA: perfluorodecanoic acid, PFDoDA: perfluorododecanoic acid, PFTrDA: perfluorotridecanoic acid.
[a] Adjusted for maternal factors (age at delivery, parity, educational level, alcohol consumption, smoking during pregnancy, pre-pregnancy BMI, logFT4).
[b] Adjusted for maternal factors (age at delivery, parity, educational level, alcohol consumption, smoking during pregnancy, pre-pregnancy BMI).

of exposure levels, a Taiwan Maternal and Infant Cohort Study that investigated mothers in the third trimester between 2005 and 2006 found that the median levels of four predominant PFASs (PFHxS, PFOS, PFOA, and PFUnDA) were 0.81 ng/mL, 9.65 ng/mL, 1.54 ng/mL, and 1.70 ng/mL, respectively (Wang et al., 2014). Furthermore, a Korean study of third-trimester mothers investigated in 2008–2009 reported corresponding median levels of the same PFAS of 0.55 ng/mL, 2.93 ng/mL, 1.46 ng/mL, and 0.60 ng/mL, respectively (Kim et al., 2011). In our study, we also used maternal blood samples obtained in the third trimester during 2002–2005 and found levels of these PFAS to lie between those of the two previous studies. We noted, however, that levels of PFAS with longer carbon chains (≥9) in this study were higher than those in the two previous studies (Wang et al., 2014; Kim et al., 2011).

TAs are found in 5–15% of women of reproductive age (van den Boogaard et al., 2011). In the current study, 9.0% of mothers were TPOAb-positive and 15.8% were TgAb-positive, which were almost the same proportions as previously reported. We previously reported that maternal PFOS was associated with lower maternal TSH and higher neonatal TSH in our other cohort (Kato et al., 2016). In the current study, we assessed effect modification by maternal TA status which was conducted in limited number of studies (Webster et al., 2014; Webster et al., 2016; Preston et al., 2018; Reardon et al., 2019) on the basis of

"multiple hit hypothesis" proposed by Webster et al. (2014) postulating that participants in TA-positive group might by more susceptible to thyroid disrupting effects by PFAS. Webster et al. (2014) reported that PFAS exposure was associated with increased maternal TSH among women with high TPOAb, while Preston et al. in Project Viva and Reardon et al. (2019) showed that PFAS were inversely associated with maternal TSH and FT4 levels in TPOAb-positive group. No analysis on neonatal THs has been conducted to explore different effects of maternal TA levels.

In maternal TH analysis, current study found that significant positive associations between PFASs and FT3 in both TA groups. On the contrary to the postulation, our result did not find that TA-positive mothers were more susceptible than TA-negative mothers. Reardon et al. (2019) suggested the susceptibility for PFAS effect on THs in TA-positive mothers might be different depending on the gestational stage. The timing of blood collection for TH measurements may be an important factor, since circulating TH levels during pregnancy change dramatically during gestational weeks (Webster et al., 2014; between gestational weeks 15–18, Preston et al., 2018; median, 9.6 weeks of gestation, and current study; 11.35 weeks of gestation). Fetal thyroid glands begin to secrete hormones after the second trimester of gestation (de Escobar et al., 2004; Obregon et al., 2007). During early pregnancy, fetuses rely on maternal THs, and the disruption of maternal TH homeostasis can affect both maternal and fetal health. Deficiencies or imbalances in maternal THs likely disrupt the normal neurological development of fetuses; therefore, we investigated the effect of maternal THs on fetuses in their early gestational stages. The current analyses of the associations between maternal PFAS levels and maternal THs were designed as a cross-sectional study. PFASs have long half elimination time as reported in Olsen et al. (2007). Therefore, we believe that PFAS levels at later gestational stage could also reflect the PFAS levels at early gestational stage. Additionally, we included TgAb-positive mothers in TA-positive group, while previous studies measured only TPOAb. We included TgAb-positive women because TgAb status was considered to be important as effect modifier to explore "multiple hit hypothesis". Unfortunately, we are unable to further speculate the differences as those previous studies did not measure TgAb. Webster et al. (2016) reported the joint effect of high TPOAb and low iodine exposure in the PFAS-TH relationships. Other factors should be considered as one of the effect modifier as well as TA status in the further study.

There are some potential mechanisms of thyroid disruption by PFAS; competitive binding to TH binding proteins (Weiss et al., 2009) and the change of hepatic clearance (Yu et al., 2009), leading to decrease of T4 and Possible mechanism of the positive association between PFAS and FT3 have been proposed to be the up-regulation of the deiodinase enzyme which converts T4 to T3 (Yu et al., 2009). In our study, PFHxS associated with higher FT3 with and higher FT4 ($p < 0.010$), while PFNA associated with higher FT3 and lower FT4 (not significant). The current results suggest the possibility of different mechanism between PFHxS and PFNA, and different susceptibility between TA-positive and negative group.

Regarding neonatal TH analysis, Kim et al. (2011) found a negative correlation between maternal PFOS and fetal total T3, and between maternal PFTrDA and total T3 and T4 levels in fetuses; moreover, maternal PFOA positively correlated with fetal TSH among 44 South Korean participants. A Dutch study ($n = 83$) found that a high level of PFOA in cord blood was associated with increased total T4 levels in heel prick blood among girls (de Cock et al., 2014). Furthermore, we previously reported the positive association between maternal PFOS and boy's heel prick TSH (Kato et al., 2016), which was also seen among all boys in the current study. Current results support the hypothesis that maternal PFAS exposure disrupt neonatal TH levels as shown in previous studies, though our results cannot be compared directly to others because previous studies did not take stratification of maternal TA status into account as mentioned above. In addition, current study suggests that maternal TA status might affect neonatal susceptibility of TH disruption; in particular, p-interaction was significant in the associations between maternal PFTrDA and girl's FT3 shown in Table 6. However, the directions of B in linear regression analysis are almost the same between in TA-positive and TA-negative group (Supplemental Tables 4 and 5). Ultimately, it remains unclear how maternal TA status might modify the relationships between PFASs and neonatal THs. The relationships should be evaluated repeatedly in other cohorts.

We note that this is the first study to examine the PFAS association with TPOAb and TgAb levels in an epidemiological study. Regarding other chemical compounds, some previous studies showed the positive associations between poly chlorinated biphenyls (PCBs) and TA levels (Langer et al., 1998; Schell et al., 2009). Therefore, we hypothesized that PFAS positively associated with TAs. We found that positive associations were found between maternal PFAS and girl's TgAb only in maternal TA-positive group. In contrast to our hypothesis, however, inverse associations were found among boys in maternal TA-negative group. Additionally, we observed a significant inverse association between PFOA levels and TPOAb in maternal blood, though this significance disappeared when stratified by maternal TA status, positive or negative. Although PFOS and PFOA have been reported to decrease the TPO's activity (Song et al., 2012), the mechanism of interaction between PFAS and TAs remains unclear. Considering that TPOAb and TgAb inhibit initial TH biosynthesis, there was a possibility that our findings of higher FT3 and FT4 levels in relation to some PFAS might be attributable to decreased TPOAb among mothers and TgAb among boys. However, mediation analysis showed no significance of TA mediating effect (Data not shown). Therefore, it is difficult to propose plausible mechanisms underlying the observation. According to Langer et al. (1998) which found positive association between PCBs and TPOAb, highly lipophilic compounds may facilitate the interaction between autoantigens and circulating immunocompetent cells in the thyroid by accumulating in the cell membranes, damaging membranes and cellular structures. In the current study, results support immunomodulative effects of PFASs as well as PCBs. Moreover, our result of lower TAs indicates PFAS immunosuppressive properties and is consistent with lower risks of allergic diseases and higher risks of infectious diseases shown in our previous report (Okada et al., 2014; Goudarzi et al., 2016a; Goudarzi et al., 2017b). While these antibodies are involved in autoimmune diseases such as Hashimoto's thyroiditis and Graves' disease, it remains unclear whether altered TPOAb and TgAb levels in relation to PFAS as we showed leads to a reduced risk of thyroid autoimmune diseases in clinical situations. Further studies are necessary to elucidate the mechanism of PFAS immunomodulative actions.

With respect to neonatal analysis, we found the sex differences between maternal PFAS and neonatal thyroid status. In maternal TA-negative group, higher TSH, lower FT3 were significantly associated with maternal PFAS among boys. In contrast, maternal PFAS were related with lower TSH and higher FT3 among girls. Furthermore, boy's TgAb were inversely associated with PFAS only in maternal TA-negative group, while girl's TgAb were positively associated only in TA-positive group. Higher TgAb levels among girls supports the higher prevalence rates for thyroid-related autoimmune diseases among women (Vanderpump, 2011). Additionally, our findings indicate that maternal TA status might work as the effect modifier more strongly among girls. Sex-based differences still remain to be explained. One hypothesis is that PFAS are eliminated faster in females than in males, as was previously shown in animal and human adult studies (Lau et al., 2007; Zhang et al., 2015). However, it is unclear whether faster elimination among females is applicable to fetal exposure to PFASs.

Other than being the first investigation of its kind, a major strength of our current study was its prospective design that allowed us to estimate the effects of prenatal PFAS exposure on fetal thyroid functions using prenatal and perinatal blood samples. Nevertheless, current results should be interpreted cautiously because we found associations

which did not imply causality. However, there were several limitations as well. First, maternal TPOAb was detected in only 67.3% of blood samples; although we assigned a value that was 50% of the LOD in the linear regression models for parameters that were not detectable, our results might not reflect the actual disruption by PFAS exposure. Second, our results might not be extrapolated to the general population, as we included a limited number of participants in the original cohort because cord blood samples were only obtained from neonates who were delivered via vaginal birth. Moreover, we also excluded mother-neonate pairs without maternal TA data. We compared the mothers' and children's characteristics of participants in this study, the original cohort for which included 2985 subjects with PFAS data (not shown). We did not observe significant differences in maternal characteristics, although children had a higher gestational age and a heavier birth weight. Although the median levels of total PFAS in maternal serum did not significantly differ between the analyzed participants (12.46 ng/mL) and comparison group (12.48 ng/mL), it is possible that healthier children were included in our analyses, which may have led us to underestimate the effects of PFAS. Third, we did not include all possible confounders in our regression analyses owing to the lack of some data. While we measured the levels of THs from cord blood in this study, it is important to note that hormone levels dramatically change between the end of gestation and the postnatal periods, and the levels of THs measured in the cord blood may be affected by various factors such as diurnal cyclicity, gestational week, duration of labor, placental weight, and the presence of pre-eclampsia (Hollier et al., 2014; Keelan et al., 2012); we did not have access to all these data. Although we checked for seasonal variations in hormone levels and found no significant differences, our regression analysis results might not reflect the seasonal changes in hormone levels accurately. Of note, the results of multiple comparisons should be carefully considered because there is a 5% chance of incorrectly rejecting the null hypothesis (Hubbard, 2011). However, we did not employ any methods to counteract any multiple comparison errors because they would have increased the probability of false negative results.

5. Conclusion

In summary, maternal PFASs was associated with higher maternal FT3 in both maternal TA-negative and positive groups. Maternal PFOA showed inverse association with maternal TPOAb, of which significance was not found after stratified by TA status. In boy neonates, prenatal PFAS showed positive association with TSH, and inverse associations with FT3 in maternal TA-negative group, while prenatal PFAS was associated inversely with TSH in maternal TA-positive group. In girls, prenatal PFAS showed inverse association with TSH, and positive associations with FT3 in maternal TA-negative group, while prenatal PFAS was associated inversely with FT4 in maternal TA-positive group. Maternal PFAS was associated with lower boy's TgAb only in maternal TA-negative group. On the other hand, maternal PFAS showed positive associations with girl's TgAb only in maternal TA-positive group. These results suggest thyroid disrupting effects of PFAS exposure, even at relatively low levels, on not only hormones but also antibodies might show different susceptibility depending on maternal TA levels. Such studies should also include long-term follow-up to investigate the fetuses' neurodevelopment and elucidate the outcomes of altered hormone levels at the fetal stage.

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Declaration of competing interest

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

Financial interests

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105139.

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