**3.5. Association between PFCs exposure and thyroid disfunction:** **epidemiological studies**

In the context of previous work of experimental evidence of PFCs reducing T3 and T4 in rats and monkeys (Butenhoff et al. 2012; Chang et al. 2009; Dong et al. 2016; Gutshall et al. 1988; Lau et al. 2003), multiple occupational and community-exposed epidemiological studies have already investigated more clinical markers of thyroid function as well (e.g, THs, thyroid-related proteins, thyroid diseases and subclinical symptoms), usually in cross-sectional designs. The nature of the association between PFCs and thyroid functions in human body was even more inconsistent, which made us more confused.

TH concentrations of the study population are summarized in Table xx. Among the general population, the serum T3 and T4 levels are sensitive indicators of thyroid function, which were supposed within the laboratory reference range of between 1.34-2.73 nmol/L and 78.4-157.4 nmol/L, respectively. In the general case, the concentration of total T4 in the normal human serum is about 90 nmol/L among general population (Fromme et al. 2009). The serum TSH concentration reference range was 0.34-5.60 mIU/L, which could assist in the diagnosis of hyperthyroidism, hypothyroidism and thyroiditis and so forth (Ji et al. 2012). The values identified to be above and below the laboratory reference range were deemed to be abnormal indicators of thyroid regulation.

Biomonitoring studies of serum PFCs levels show major differences among occupational and other lower-environmental groups. Most studies evaluated associations with different levels of potential PFCs exposure, thereby enabling at least rudimentary exposure-response analysis. Take PFOS as an example, the PFOS geometric mean level was 941 ng/mL among fluorochemical workers at the Decatur plant, U.S in 1998 (GW et al. 2003) and the median was 1,000 ng/mL at the same plant in 2000 (Olsen et al. 2007). At the Antwerp and Cottage Grove plants, U.S, the median levels were 550 and 450 ng/ mL, respectively (Olsen et al. 2007), while the geometric mean level among background-exposed film division workers at the Decatur plant was 136 ng/mL (GW et al. 2003). By contrast, median serum PFOS levels were up to two orders of magnitude lower in Ohio and West Virginia residents near the Parkersburg plant (approximately 20 ng/mL in 2005 - 2006), where industrial use of PFOS did not occur (Frisbee et al. 2009), comparing with US general population participants in NHANES (30.2 ng/mL in 1999-2000 and 13.6 ng/mL in 2007-2008) (Kato et al. 2011), and U.S Red Cross adult volunteer blood donors (35.8 ng/mL in 2000-2001 and 8.6 ng/mL in 2010) (Olsen et al. 2012). Again, great differences of PFCs exposure in populations must be considered when contemplating the plausibility of observed probable associations in low-exposed populations, but not only in occupational or general settings.

To date, there is no consistent finding across most of the studies that even provide clear-cut evidence supporting/opposing a causative role of PFCs in thyroid axis perturbation. For instance, in one study no statistically significant associations were observed between the concentrations of PFCs with FT4 or TSH (Bloom et al. 2010), while PFOS concentrations were found to be negatively associated with TSH, and positively with FT4 concentrations in another study (Dallaire et al. 2009). A study from Taiwan also found positive correlations between PFNA with T3 and FT4 levels, which is similar to findings reported in another Taiwanese cohort of young adults (Lin et al. 2013; Wang et al. 2014). Here, we aim to summarize previous systematic epidemiologic evidence regarding the different exposure settings, getting the benefit of a relatively large number studies and publications discussing human thyroid effects on the PFCs contaminants during the past decades.

***3.5.1. General population exposure***

Epidemiologic data were collected mainly among general population and have not found consistent effects on incidence and mortality of human thyroid diseases. Although prior epidemiologic studies on PFCs and thyroid function have reported mixed results, some analysis did indicate correlations between PFCs and THs levels. Several studies, to date, found thyroid disease to be associated with concentrations of some PFCs among members of the general population.

An epidemiological study about the general U.S adult population by NHANES U.S general adult population from 1999-2000, 2003-2004, and 2005-2006 examined the association between higher PFOA and PFOS concentrations and thyroid diseases (and being on thyroid-related medication) in the representative study samples (Melzer et al. 2010). In this study, the prevalence of reporting any thyroid disease was 16.18% (n = 292) in females and 3.06% (n = 69) in males, as high as prevalence of current thyroid disease with related medication (9.89% (n = 163) in females, and 1.88% (n = 46) in males, respectively). The NHANES data of this paper showed a strong effect on self-reported thyroid disease (no exposure data at the time of diagnosis, and not distinguishing between hypothyroidism or hyperthyroidism) at very low PFOA levels, which was not easily interpreted in the context of the other studies though. Discrepancy sometimes occurs on analogous study. Another NHANES wave from 2003-2006 to 2007-2010 researched by Coffman et al. found a persistent association between PFOA levels and a history of thyroid disease in women, and an association between PFOS levels and a history of thyroid disease in men. Notably, in women the crude odds ratios (ORs) comparing thyroid disease history across PFOA exposure groups demonstrated a near exposure-response type relationship, that is, with increasing PFOA exposure corresponding to increasing odds of thyroid disease history. Increased log-transformed serum PFOA levels were also associated with higher odds of a history of thyroid disease in women (regression coefficient per 1 ln unit [β]=0.39, 95% CI: 0.05-0.73, p = 0.028), but not in men (Coffman 2013). Not coincidentally we were unable to directly determine a temporal link between the PFCs exposure and the thyroid outcome by these data, because the disease outcome had already occurred. A Korean study with 13 PFCs serum levels among 786 adults living in Seoul demonstrated the positive associations between FT4 and PFOS, PFNA, PFHxS, PFDA, and PFOA. Significant correlations were found between FT4 and PFNA, PFOS, PFDA and PFDS among male participants (p < 0.05), FT4 was significantly associated with PFBS, PFHxA, PFHxS, PFNA, PFOS, PFDA, and PFUnDA (p < 0.05) among females (Seo et al. 2018). A possible explanation for this correlation observation is that the presence of PFCs in human body may disrupt TH homeostasis, for PFCs may affect basal metabolic rate and protein synthesis. Unlike FT4, TSH showed inconsistent correlations with PFCs concentrations in participants with no statistically significant correlations, which assumed consequently was not directly affected by PFCs. Melzer et al. attributed the associations between FT4 and PFCs concentrations to that PFCs in the body could potentially interfere with binding on the FT4 carrier proteins and when FT4 could not bind to these proteins, it just remained in the blood and was detected in high concentrations (Melzer et al. 2010). Likewise, a study selected 1181 subjects (aged 20 years) from the NHANES 2007-2010 demonstrated the direct association between higher serum PFOA concentrations and TT3 in females, and between higher PFHxS and TT4 and TT3 in females, and the inverse association between PFHxS and FT4 in male participants. The authors reported a higher risk of subclinical hypothyroidism in females with increased PFCs exposure especially PFOA ([Wen et al., 2013](https://www.sciencedirect.com/science/article/pii/S0013935116300780" \l "bib47)). Data from NHANES 2007-2008 found TSH levels increased with increase of PFOA levels (p = 0.01). Despite no statistically significant associations was found between the levels of FT3, nor FT4 with the levels of any of the detected six PFCs, the levels of TT3 were found to increase with PFOA (p = 0.01) and TT4 were found to increase with increase in PFHxS levels (p < 0.01) (Jain 2013). Among adult women in the NHANES 2011-2012 wave, Lewis et al. found a positive association between FT3, TT3, and FT4 and serum concentrations of all four PFCs (PFOS, PFOA, PFHxS, PFNA) in women, but other THs concentrations were not associated with PFCs in women nor in adult men (Lewis et al. 2015). Dallaire et al. examined 41 contaminants including PFOS, in relation to total T3, FT4, and TSH concentrations in plasma from adult Inuit (n = 623) from Nunavik, Canada and they found that PFOS was negatively associated with TSH, negatively associated with TT3, but positively associated with FT4 (Dallaire et al. 2009). in China, Li and his colleagues detected 202 human serum samples of the general population, reporting PFOS and ∑8PFCs were significantly negatively correlated with FT3 and FT4 and positively correlated with TSH (Li et al. 2017). A Taiwan adolescent and young adult population (aged 12-30 years) found that a higher serum concentration of PFNA was associated with elevated serum FT4, which hint at an effect for low-dose PFNA in humans, although the potential biological significance between PFNA and FT4 is small and merely subclinical in this Taiwan general population (Lin et al. 2013).

However, there have been only few reports that suggested entirely null associations between concentrations of PFCs and concentrations of thyroid hormone in the general population. For example, negative associations were found between FT3, TSH and PFOS, PFOA and PFHxS levels in general population, meanwhile PFOS and ∑8PFCs were significantly negatively correlated with FT3 and FT4 and positively correlated with TSH in hypothyroidism and hyperthyroidism group (Li et al. 2017). No significant associations between any of the frequently detected PFCs and TSH, FT3, or FT4 were observed (Heffernan et al. 2018). In a small community study of New York State anglers, at much lower exposure levels (PFOA serum geometric mean = 1.33 ng/mL), potential associations were investigated between serum concentrations of 8 measured PFCs and levels of TSH and FT4. As a consequence, no associations were found, but study power was very low (Bloom et al. 2010). The robustness and generalizability of this study is limited given the small sample size of the cohort (n = 31).

The vast majority of reported a positive association between PFCs and FT4, or thyroid diseases incidence or prevalence among general exposure population, which was consistent with the hypothesis of probable effect by their own authors in advance. Whereas this view will not generalizable to other populations or be added to existing literature in the same age/gender range, so shall a universal truth be.

***3.5.2. Occupational exposure***

Previous studies noted that workers in fluorochemical production plants was a subgroup that loaded an exceptionally high body burden of PFCs. In these occupational-settings analysis, researchers usually compared workers’ clinical chemistry and THs results in relation to their serum measurements of PFCs, either PFOA or PFOS in most cases. (Emmett et al. 2006; Gao et al. 2015; GW et al. 2003; Olsen and Zobel 2007; Steenland and Woskie 2012; Winquist and Steenland 2014; Zhou et al. 2014). In most cases, workers occupationally exposed have serum levels of both PFOA and PFOS approximately 1-2 orders (sometimes might as high as 4, for example, the Chinese occupation cohort detected in 2008-2012 with median serum concentrations of 764, 427, and 1725 ng mL−1, respectively (Fu et al. 2016)) of magnitude higher than those reported in general population. This chapter included investigations of workers with occupational exposure and community members predominantly without direct occupational exposure to PFOA and/or PFOS. Most of high-exposed populations across the world were recorded in C8 health project, U.S (see website http://www.c8sciencepanel.org/index.html), which was conducted as part of the settlement from a class-action lawsuit against DuPont with the purpose of investigating the potential human health effects of PFOA (or C8) exposure from contaminated drinking water adjacent the DuPont plant at Parkersburg West Virginia, U.S. During 2005-2013, related epidemiological studies were conducted in the Mid-Ohio Valley communities by members of the C8 Science Panel enrolled 69,030 people (an estimated 80% of eligible subjects; 81% of those aged 20 years and older) who lived, worked, or attended school for at least 1 year in one of the six contaminated water districts near the Parkersburg plant between 1950-2004. The settlement also established that a group of public health scientists would assess whether or not there is a probable link between C8 exposure and six disease categories in the community members. The Science Panel concluded that there was a probable link to C8 exposure and diagnosed thyroid disease.

Olsen et al. reported positive associations between PFOA or PFOS and FT3 serum levels (Olsen et al. 2003; Olsen and Zobel 2007). In 2007, the authers indicated a negative association between PFOA and FT4 serum levels, and a positive association for PFOA and T3, without changes in TSH serum levels (Olsen and Zobel 2007). 93% of the cohort participants were male workers, whose serum PFOA concentration analyzed was as amazingly high as median 1,100 ng/mL, although the authors concluded that the results with only THs testing were not of clinical significance. In contrast to the study by Olsen et al in 2007, there were no correlations between PFCs and serum FT3 and FT4 among fishery employees from Tangxun Lake, China (Zhou et al. 2014), of which arithmetic mean concentrations of PFOS (n = 39, 11 400 ± 6760 ng/mL) were even more than 1 order of magnitude higher than those in retired fluorochemical plant workers of 3M Company (Olsen et al. 2007). Although it is not a traditional “occupational” elevated exposure in the sense that the fishery employees are being exposed as a result of indirect contact or inhalation of PFCs. Currently there are very limited studies comparing PFCs concentrations between patients with thyroid disease and control group, therefore, we cannot clearly explain these results with low statistical power.

Occupational exposure contributed to ∑PFCs body burden to a greater or lesser extent for workers in PFCs chemical manufacturing department with long occupational exposure durations. Thus PFC exposure assessments should also evaluate the workplace as a potential source, where workers not directly involved in manufacturing PFCs, even when workplace exposures are assumed to be low or moderate. Tanner et al. observed 25% higher serum PFOS and 80% higher PFOA levels in 154 older adults in New York State, U.S (nobody reported PFCs chemical manufacturing work but 68 participants admitted work in occupations and industries known related to PFCs), compared to NHANES general population in the same period (Tanner et al. 2018).

Added to existing literature, the significant high serum PFCs levels were generalizable to other men and women in the same older age range, even if this study didn’t involve in any thyroid parameters. These occupational researches elaborated that human thyroid imbalance is associated with past or recent occupational or high-environmental exposure to these compounds.

***3.5.3. Population exposed to high environmental levels of PFCs***

PFCs exposure might also occur in high-environmental settings outside of the occupational exposures resulting from direct PFCs manufacturing. Low-level continuous exposure to PFCs, occurred from working in and around the general production environment without direct involvement in chemical production might cause profoundly adverse effects. The two communities have been exposed via water contamination coming from adjacent industrial plants. As reported by the Minnesota Department of Health in 2009, the mean PFOA in Minnesota was 15 ng/mL, whereas the mean was over 4 times higher (82 ng/mL) among the environmental exposed residents in Mid-Ohio Valley, 2005 (Emmett et al. 2006; Frisbee et al. 2009; Steenland et al. 2010; Steenland and Woskie 2012).

All around the world, except occupational cohorts, the largest populations above PFCs background levels are two communities in Minnesota and West Virginia, U.S, both in the ambient environment of PFOA manufacturing facility.

* **No association between PFOA exposure and THs**

Earlier epidemiological studies show no associations between PFOA and thyroid status including TSH in highly exposed West Virginia residents (Emmett et al. 2006), and thyroid hormone status in repeated measurements of occupationally exposed workers (Olsen et al. 2003). Olsen et al. (GW et al. 2003) conducted a cross-sectional analysis that included two plants (3M Company facilities: Antwerp, Belgium; Decatur, Alabama, U.S)) with 255 and 263 workers, respectively. Multivariate regression analysis by quartiles of PFOA or PFOS exposure showed no significant association of either compound with T3, T4, or TSH. A continuous regression suggested a slight positive association between log PFOA and log T3 (p-value = 0.01); however, the contribution of this association to the variance of the outcome was negligible (partial R2 = 0.01). Emmett et al. investigated the association between PFOA and thyroid health outcomes in 371 community residents with high serum levels due to contaminated drinking water. No significant positive association between serum PFOA and biomarkers of thyroid effects from PFOA in a sample of residents from a community with markedly elevated serum PFOA (median concentration: 354 ng/mL, interquartile range: 184-571 ng/mL), after long-standing environmental exposure to PFOA. Though study individuals with thyroid disease (N = 40) had lower levels of PFOA (387 ng/mL) compared with individuals without thyroid disease (451 ng/mL), but this difference was also not statistically significant (P = 0.3) (Emmett et al. 2006). And this finding of a lack of an association just concurred with similar results from another high-exposed cohort (32,254 adults, including 3,713 workers (1,890 of whom were also enrolled in the cross-sectional C8 Health Project) and 28,541 community members) (Steenland and Woskie 2012). An occupational study reported analyses of THs in relation to PFOA among 552 employees in three plants (3M Company facilities: Antwerp, Belgium; Cottage Grove, MN, U.S; and Decatur, AL manufacturing, U.S) (PFOA median serum level, 1,100 ng/mL). A log-log regression adjusted for age, body mass index (BMI), and alcohol intake showed a negative slope for FT4 (*p* = 0.01) and positive slope for T3 *(p* = 0.05), with consistent direction of eﬀect for each plant. But for TT4 and TSH, correlations across plants and within plants were not significant (Olsen and Zobel 2007).

* **Positive association between PFOA and thyroid disturbance**

Population-based studies, generally in occupational settings have generally not found significant associations between concentrations of thyroid diseases and PFOA in serum, but such associations were reported in a few studies(Coffman 2013; Lewis et al. 2015). A children cohort based on C8 project, U.S found that serum PFOA concentrations are positively related to hypothyroidism, PFOS and PFNA relevantly with T4 and TSH levels, although PFOA was uncorrelated for measurement absence of children T3 and FT4 levels (Lopez-Espinosa et al. 2012). A large epidemiological study conducted in the similar place with high-environmental PFCs level showed that higher PFOA exposure was associated with incident functional thyroid disease, of which contained 32,254 participants, 3,633 cases reported functional thyroid disease (excluding neoplasms, congenital disease, nodules without functional changes, cysts, and unspecified type). And notably, the hazard ratios suffering thyroid diseases across cumulative exposure was higher in women than men (Winquist and Steenland 2014).

* **Sex-specific effect on PFCs and thyroid status**

Thyroid disease in the U.S is on the rise and there is a sex-specific difference in the percentage of individuals affected (i.e., 16% of adult women and 3% of adult men have thyroid disease) (Melzer et al. 2010). Consistent with the animal data of mean PFOA and PFOS concentrations, it was long been indicated lower levels in women than men, highlighting the importance of stratifying data analyses by gender (Knox et al. 2011a). Adult women in the highest quartile of PFOA exposure had statistically increased odds ratio (OR) of having thyroid disease *vs* women in quartile one or two; non-significant but similar trends were also seen in adult males who were statistically less affected by thyroid disease than women. With PFOS exposure in adult males, the highest quartile PFOS exposure was associated with statistically increased OR of thyroid disease *vs* quartile one and two PFOS exposure, while PFOS had no significant effect on OR for thyroid disease in women (Melzer et al. 2010). A study reported that associations were observed for hyperthyroidism and hypothyroidism among women in high-PFOA exposed communities, and suggested an increased hazard of hypothyroidism among men (Winquist and Steenland 2014). This finding was consistent among children of between 3 and 18 years of age (n = 150), serum PFCs levels were found remarkably higher among boys > 10 years of age than girls (Kang et al. 2018).

Mechanisms of sex specific association especially warrant further study. One interpretation for the gender differences is menstrual bleeding. In human beings, PFCs are eliminated via both menstruation and renal elimination, and the volume of blood is restored before the levels of the levels of toxicants. Indeed, earlier work in this cohort demonstrated that perfluorocarbon concentrations in women in perimenopausal and menopausal age groups were higher than those in younger women (Knox et al. 2011b). Besides, due to sex-specific elimination pathways that are unique to women, the Ritter model scenarios indicated that the elimination half-life for men was 1.2 times longer than for women when menstruation was considered as a loss process, but 1.3 times when not, albeit, elimination by menstruation at least explained 30% of the discrepancy between men and women (Wong et al. 2014).

Besides, sex steroids modulate thyroid hormone by altering the clearance of T4-binding globulin (TBG) produced in the liver, suggesting gender should be an important factor in human studies of thyroid function in response to PFCs exposure (R and BM 2009). A study containing two large NHANES waves (2007-2008, 2009-2010) provided some additional evidence that the highest serum concentrations of PFOA and PFOS were still associated with a history of thyroid disease in U.S adults (Coffman 2013), and suggested that prevalence trends remained significant when measuring current thyroid disease in women across exposure quartiles (Barbara Pirali and Danilo Cottica 2009). The NHANES data showing an association between serum PFOA and women with thyroid disease were robust, and reverse causation was even unlikely because this association was still seen in the medicated population of those with the disease (Melzer et al. 2010). More recently, a study demonstrated a positive association between serum PFOA levels and serum T3 in women and between PFHxS and serum T4 and T3 in women and the inverse association between PFHxS and FT4 in men (Wen et al. 2013). Consistent with previous studies (Knox et al. 2011a; Melzer et al. 2010), a negative association was found between FT4 and PFHxS in men without the concomitant increase in TSH that would be expected through feedback stimulation (Wen et al. 2013).

Overall, studies in high-environmental exposed populations, serum PFOA concentrations positively related with of potential adverse thyroid status (e.g, hypothyroidism). Future studies aimed at characterizing high PFCs exposure in population cohorts should consider obtaining detailed work histories to strengthen exposure assessments since residence histories would be likely to precede more recent regulatory phase-outs of PFOA and PFOS, and because these chemicals were relatively long-lived in serum. This may be important in occupational and high-environmental population, particularly in countries that have not yet phased out long-chain PFCs completely.

***3.5.4. Pregnant women and children exposure***

Widespread exposure to PFCs among human populations raises concerns about its potential public health consequences, and the association between PFCs exposure and fetal growth is such one. But published epidemiological findings are not consistent, have generally focused on adults, and have been cross­sectional in nature——leaving a gap in the understanding of possible PFCs eﬀects in pregnant women and children. THs are vital regulatory factors for the growth and development of human beings and are controlled by the HPT axis. For infants, THs play an important role in the development and regulation of the reproductive system, and in the perinatal development of the central nervous system. And they also act crucial role in regulating metabolism and promoting normal cardiovascular, reproductive, and nervous system functions. Absence of THs reduces neuronal growth and differentiation in the cerebral cortex, hippocampus, and cerebellum, which are especially important during brain maturation and the development of the fetus and children. (Aas et al. 2014; Song et al. 2012). This part focuses on PFCs and thyroid disruption during the gestation and childhood periods.

As for fetuses and infants, two exposure pathways of PFCs, including maternal-fetal transmission and breast-feeding transmission, have attracted intensive attention in recent years (Kang et al. 2018; Kim et al. 2011a; Raleigh et al. 2014). Based on the mother-infant pair studies, it appears that certain PFCs are transferred to a considerable extent through the placental barrier to the fetus. During the first part of pregnancy, the fetus relies entirely on transplacental transfer of maternal THs and thus on a normal maternal thyroid function, and maternal thyroid homeostasis is also contributing substantially to fetal development during the remaining part of pregnancy (Zhang et al. 2018).

For mothers, biomonitoring studies of maternal serum levels showed major differences of mothers’ environmental background PFOS and PFOA exposure, with diverse PFC-industrial technology and history so far. One investigation indicates that among pregnant Danish women, mean blood plasma concentrations of PFOS and PFOA were as high as 35.3 and 5.6 ng/mL, respectively (Fei et al. 2009). In the pregnant Canadian women wave, mean blood serum levels of PFOS and PFOA in blood serum were 18.3 and 2.5 ng/mL, respectively (Monroy et al. 2008). A sample of 118 mother-infant pairs was obtained from the Taiwan Birth Panel Study (TBPS), which showed that PFOA concentration in the Taiwan pregnant cohort was 3.14 ng/mL (Tsai et al. 2017). Investigators revealed that plasma PFOA and PFOS in pregnant women from Shanghai, China, were the predominant PFCs with profoundly high median concentrations (19.97 ng/mL and 10.81 ng/mL, respectively) (Tian et al. 2018). Several studies have reported that maternal sociodemographic characteristics, including maternal age, educational level, household income, and pre-pregnancy body mass index (BMI), might be associated with PFCs concentrations in pregnant women, but the results have been inconsistent across different countries or regions. Pregnant women who were older, multiparous, well educated, passive smokers, with lower per capita household incomes, and had lived in rooms decorated within the past two years had higher PFCs concentrations (Fisher et al. 2016; Jeddy et al. 2017; Manzano-Salgado et al. 2015; Tian et al. 2018).

* **Different trans-placental ratio of specific PFCs**

The observation that PFCs in maternal blood could pass the placental barrier to fetal blood PFCs concentrations resulting a significant decline during pregnancy was consistent with the results of many studies reporting transplacental transfer of PFOS and PFOA (Mclaughlin et al. 2007; Midasch et al. 2007). Significant positive correlations have been found between concentrations of PFCs in paired samples of maternal whole blood and placenta, and between placenta and cord blood (Zhang et al. 2011). Different PFCs may exhibit a different trans-placental ratio, and as neonates are exposed to PFCs through maternal exposure, the transfer ratio of PFCs may interfere with the thyroid hormone levels of neonates. Several studies have demonstrated the finding that (1) maternal blood PFOA and PFOS can pass the placental barrier to foetal blood, (2) cord blood PFOA concentrations are similar to those of maternal blood but PFOS concentrations are less similar and that (3) competing mechanisms appear to be involved in the trans-placental transfer efficiency of specific PFCs, and carboxylates (i.e. PFOA and PFNA) transferred more efficiently across the placenta than sulfonates (i.e. PFHxS and PFOS). To this topic, while PFTrDA has the greatest ratio, PFDA has a ratio less than those for PFOA and PFNA (Bjerregaard-Olesen et al. 2016; Fisher et al. 2016; Monroy et al. 2008; Preston et al. 2018). Many epidemiological studies from different countries have also validated these mechanisms of PFCs trans-placental transfer. A highest transport efficiency of PFOA both through placental barrier and lactation was observed among 50 pairs of Chinese women and their newborns, and the latter period was found more efficient compared with the former (Liu et al. 2011a). In a study of Canadian mother-infant pairs (n = 101 for pregnant women, 105 for matching infants), the authors reported ratios of concentrations in maternal blood serum to that in cord blood serum for PFOA, PFNA, PFHxS, and PFOS were 1:0.87, 1:1.18, 1:1.25, and 1:0.44, respectively (Monroy et al. 2008). Maternal plasma to cord ratios were above 1 in a Spanish birth cohort (n = 66 mother-child pairs, PFHxS: 2.35 [95%CI: 2.05, 2.70], PFOS: 3.33 [3.05, 3.62], PFOA: 1.37 [1.27, 1.48], PFNA: 2.39 [2.18, 2.63]), and maternal serum to cord ratios were alike (Jeddy et al. 2017). All of these previous studies found that the trans-placental transfer ratio of PFCs did not scale linearly with the chain length of the target compounds, and the levels of PFOA in cord blood were more parallel to levels in maternal blood than PFOS. The relatively great efficiency of the trans-placental movement of PFCs has potential clinical implications since the fetus might be more susceptible to alteration in thyroid hormone homeostasis during critical periods of development due to control of availability of cholesterol and triglycerides, which support cellular differentiation and fetal development (Inoue et al. 2004).

* **PFCs effects on thyroid function in mothers**

Albeit existing studies have reported a mixed pattern of associations between maternal PFCs and THs concentrations, most of investigators supported the hypothesis that prenatal exposure to PFCs did not influence thyroid function in mothers, which many results turned out to be. Lewis et al. found a positive association between FT4 and serum concentrations of all four PFCs (PFOA, PFOS, PFHxS, and PFNA) considered here in women of reproductive age in the NHANES 2011–2012 survey, but other thyroid hormone concentrations were not associated with PFCs in women of reproductive age (Lewis et al. 2015). In contrast to Lewis et al., Peck et al. also reported no associations between FT4 and serum PFOS in a very small group of pregnant women (n=42), but did show an increase of TSH with higher PFOS concentrations (Peck et al. 2008). Another study in 2005-2006 among pregnant women (96 hypothyroxinemic cases (normal TSH, the lowest 10th percentile of FT4) and 175 controls (normal TSH, FT4 between the 50th and 90th percentiles)) matched on age and referring physician) in Canada showed no association of PFOA, PFOS, and PFHxS with thyroid function (Chan et al. 2011). Whereas, pregnant women during gestation with the highest concentrations of PFOS, PFDA and PFUnDA had consistently higher TSH and lower T3 and FT3 concentrations, respectively (Berg et al. 2015).

* **PFCs effects on thyroid function in young age groups**

However, the hypothesis that PFCs exposure correlated with thyroid function in newborns might be true. It could be difficult to obtain ethical permission for biological samples from healthy newborns, and therefore samples of cord blood are often used. Among infancy, results from previous studies about PFCs levels and THs most are contradictory, some researchers owing this to that neonatal TH levels may depend on various factors such as birth weight, gestational age, and mode of delivery and the timing of sampling (Kim et al. 2011a). Cord blood concentrations of PFCs, particularly PFOS and PFUnDA, to be positively associated with cord blood THs (p = 0.01) level (Tsai et al. 2017). An epidemiology study in a Dutch cohort revealed that cord plasma levels of PFOA and PFOS are associated with T4 (Cock et al. 2014). The authors of this Dutch cohort found that the cord blood PFOS concentration was negatively associated with the cord blood T4 concentration [per ln unit: adjusted β (95% confidence interval, CI) = -0.458 (-0.916, -0.001)]. In addition, there was indeed a positive association between cord blood concentrations of PFOS and TSH, but a negative association between cord concentrations of PFOS and T4 (Tsai et al. 2017). Furthermore, the level of cord blood TSH was positively associated with the cord blood PFOS concentration [per ln unit: adjusted β (95% confidence interval, CI) = 0.346 (0.101, 0.592)] (Tian et al. 2018). Moreover, a study shows that cord blood PFPeA was positively associated with cord blood T4 (p = 0.01) level in Korean newborns (Shah-Kulkarni et al. 2016). Of note, although no consistent association has been reported to date between blood PFCs and adverse thyroid health effects in low age groups, an observation in Korean infants suggests a potential association between the concentrations of PFTrDA and thyroid disfunction. Results indicated that levels of three PFCs (PFOA, PFTrDA, and PFHxS) in infants with congenital hypothyroidism (CH) has a moderate to weak correlation with antibodies, specifically thyroid stimulating immunoglobulin (TSI), which is indicative of metabolic disease (Kim et al. 2016). The correlation also occurred in young groups, PFCs was found might be related to increases in TSH among males and decreases in TSH among females during adolescence (Lewis et al. 2015). Coincidentally, a systematic review (publication: 2011-2015, 10 studies) found some evidence of a positive association between PFHxS and PFOS exposure and TSH levels measured in maternal blood, and PFNA and TSH levels measured in the blood of boys aged ≥11years (Ballesteros et al. 2017).

* **Sex-specific PFCs effects on T4 in newborns**

Interestingly, though the current data does not clearly confirm nor refute any association between PFCs exposure and TH homeostasis in sensitive population, we noticed that exposure to PFCs may exhibit sex-specific effects T4 during childhood. The sex stratified effects of PFOS on T4 were suggestive of differential effects in high-exposure groups compared with low-exposure group in male infants (Tian et al. 2018). Gender-specific associations were also reported by de Cock and colleagues, they found the results in a sex-specific manner, which showed the highest group of PFOA exposure was associated with an increased level of T4 compared to the lowest exposure group in complete models for girls, though a decreased level of T4 was observed in the second quantile (Q2) of PFOA and PFOS exposure in the crude models (Cock et al. 2014). Also, the gender-specific analysis showed that prenatal PFCs: PFPeA and PFHxS exposure significantly increased T4 (p < 0.01) and T3 (p = 0.03), respectively, while PFNA decreased TSH (p = 0.04) concentrations in newborn girls (Shah-Kulkarni et al. 2016). This mechanism probably explained why the results showed a significant association in girls but not in boys: during pregnancy, the thyroid gland and gonadal axes interacts continuously before and during pregnancy for women as well (Shah-Kulkarni et al. 2016). There is an estrogen-induced increase in TBG production, and estrogen reduces TBG clearance thereby increasing its concentration in the body, which may increase T4 concentration, while androgens have the opposite effect (Shah-Kulkarni et al. 2016).

* **Interaction between maternal/neonatal THs and PFCs**

The foetus relied on maternal THs throughout gestation and a normal supply of maternal T4 has an important protective role. Subtle individual changes like little variation in levels of maternal THs caused by PFCs even within normal reference ranges and may not be of clinical significance in the pregnant woman, probably have significant consequences for foetal health. In the newborns, TSH increases dramatically immediately after birth, peaking at 30 min, followed by an increase in both T4 and T3. A significant correlation was observed among levels of PFCs in matched maternal serum, cord serum and breast milk (Liu et al. 2011b). Most animal studies investigating associations between maternal PFCs exposure and THs in neonates found T4 reduction to be associated with PFOS exposure (Lau et al. 2007; Luebker et al. 2005; Yu et al. 2009). Those pairs, both maternal blood and cord blood, consisted of different components thus showed significant difference between profiles of individual participant, concentration and congener. Studies performed in Korea (Kim et al. 2011b) and in Taiwan (Wang et al. 2014) found that maternal PFCs concentrations were associated with cord blood THs. Kim et al. recruited pregnant females from three hospitals and collected blood samples in the third trimester and at delivery, they found maternal PFOA to be positively associated with cord blood TSH, however, there were no associations between cord blood PFOS or PFOA concentrations and T4 and TSH (Kim et al. 2011b). Moreover, in a study performed in central Taiwan, the authors collected blood samples from women during the third trimester and at delivery and found that maternal cord concentrations of PFNA, PFUnDA, and PFDoDA were negatively associated with cord T4 and T3 levels (Wang et al. 2014). In addition, in a longitudinal pre-birth cohort in Boston, Massachusetts, U.S, prenatal exposure to PFOS, PFOA and PFHxS during early pregnancy was negatively related to maternal FT4 and neonatal T4 in male infants (Preston et al. 2018). Conversely, Yang et al. found negative correlations for maternal T3 and FT3 levels with foetal PFCs levels (Yang et al. 2016). Subtle changes in the individual set point of thyroid homeostasis may have significant acute and long-term effects, especially if this occurs during sensitive developmental periods. This is particularly true for high-risk groups such as fetuses, newborns, children and pregnant women. Pregnant women and their foetus, infants and adolescence are particularly vulnerable to permanent effects on thyroid. As the major exposure pathway, maternal blood PFCs can pass the placental barrier to foetal blood and the transfer efficiency of specific PFCs differed from each other. PFCs exposure probably correlated with thyroid function in newborns, especially exhibited sex-specific effects on T4 among young age groups. PFCs/THs concentrations tended to be associated to a certain extent between cord and maternal blood/serum.

Considering all related studies, future orientation ought to demonstrate whether certain authentic linkage existed between perfluorinated substances and thyroid dysfunction in diﬀerent thyroid diseases subgroups in epidemiological studies. Participate from different population cohorts (high-exposed/general/thyroid patients and pregnant women/infants /children population) was not identical with the conclusion of a causal association between PFCs exposure and thyroid disturbance in humans. These occupational researches elaborated that human thyroid imbalance is associated with past or recent occupational or high/durable-environmental exposure to PFCs. In high-environmental exposed populations, it seemed that serum PFOA concentrations positively related with functional thyroid diseases. A positive association between PFCs and FT4, or thyroid diseases incidence or prevalence was raised among general exposure population. Maternal blood PFCs can pass the placental barrier to foetal blood, which probably correlated with thyroid function in newborns, with potential sex-specific effects among young age groups.

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