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Perfluoroalkyl and polyfluoroalkyl substances in cord serum of newborns and their potential factors

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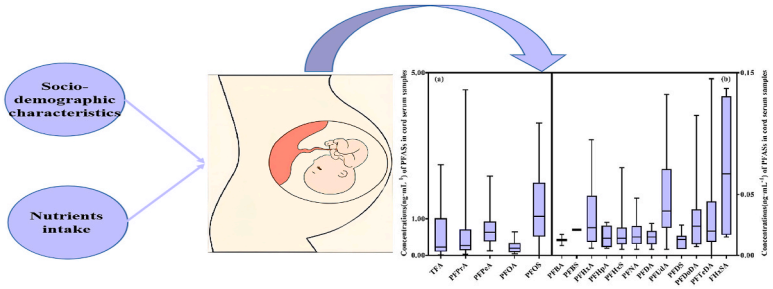
HIGHLIGHTS

- Establishment of UPLC-MS/MS for the detection of target compounds ranging from 2 to 18 carbons.
- TFA and PFPrA concentrations in human cord serum are reported for the first time.
- The levels of emerging short-chain alternatives have increased significantly.
- Nutritional supplements and diet during pregnancy may affect PFAS exposure differently.

GRAPHICAL ABSTRACT



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ABSTRACT

The demonstrated developmental and reproductive toxicity of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), coupled with the increasing production and use of emerging per- and polyfluoroalkyl substances (PFASs) has resulted in progressively higher human exposure levels. This has raised concerns about PFAS exposure levels in the fetus, which is highly susceptible to the potential effects of hazardous environmental chemicals. However, *in utero* exposure to PFASs and health implications have not been fully characterized in China. To fill this gap, we analyzed 19 PFASs in umbilical cord serum samples (n = 66). Information about the mothers and newborns was obtained through questionnaires. Associations between maternal characteristics and neonatal birth weight and PFAS concentrations were analyzed using nonparametric tests. As results, PFOA was detected in all serum samples. The highest median concentration of PFOS in umbilical serum was 1.092 ng·mL^{-1}, followed by perfluoropentanoic acid (median: 0.633 ng·mL^{-1}). Trifluroacetic acid and perfluoropropanoic acid were detected in cord serum for the first time, and their median concentrations were 0.229 and 0.266 ng·mL^{-1}, respectively. Neonatal birth weight was negatively correlated with long-chain PFOS (r = −0.319, P < 0.05), and the concentrations of perfluoroundecanoic acid and perfluorododecanoic acid were

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significantly different between the birth weight groups. Maternal age, maternal education, diet, and nutritional supplementation during pregnancy can all affect umbilical serum exposure to PFASs. These results demonstrate that legacy PFASs remain major contributors to the composition of human PFASs, while the concentration levels of emerging short-chain alternatives have increased significantly. Modifying the mother's diet may reduce the risk of intrauterine PFAS exposure. Special attention to exposure to highly novel PFASs and confirmation of potential determinants should be taken as a priority in the plan for risk management and actions in this area.

1. Introduction

Per- and polyfluoroalkyl substances (PFASs) are synthetic chemicals that include fluorine and are widely employed in industrial and consumer goods. Particularly, long-chain PFASs with carbon chains longer than eight, such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), are detectable in individuals and the environment worldwide due to their persistence and accumulation (Gomis et al., 2017; Shi et al., 2016). The Stockholm Convention on Persistent Organic Pollutants officially recognized PFOS as a persistent organic pollutant in 2005. Eight major PFOA producers signed a contract with the US Environmental Protection Agency in 2006, pledging to phase out PFOA emissions and use voluntarily by 2015 (USEPA, 2016). Long-chain PFASs with a carbon chain length of 11–14 carbons are listed as substances of very high concern by the European Chemical Agency and should be controlled (ECHA, 2014). At the second conference of the International Conference on Chemicals Management in 2009, representatives of the United States and the (Organization for Economic Co-operation and Development (OECD requested that the long-chain PFASs, represented by PFOS and PFOA, be referred to as "perfluorinated chemicals (PFCs)." PFCs are identified as an emerging policy challenge in the context of global chemical management and are called for replacement and abolition (OECD, 2014; OECD/UNEP Global PFC Group., 2013). Perfluorobutanesulfonic acid (PFBS), perfluorohexanoic acid (PFHxA), and their derivatives are examples of short-chain PFASs that have been highly promoted and used in various fields as substitutes for the original long-chain PFASs on a large scale (POPAC, 2015). Perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFHpA), and other novel long-chain PFASs fit this description. In recent years, many monitoring studies have shown that the environmental concentrations of these emerging short-chain PFASs are increasing significantly, even reaching levels comparable to those of traditional long-chain PFASs (Bao et al., 2011; Meng et al., 2015; Zhou et al., 2013). With the increased production and use of PFASs in China, precursors have attracted attention as a possible source of PFASs.

Animal studies have demonstrated that traditional PFASs (represented by PFOS and PFOA) are reproductively and developmentally toxic (Andersen et al., 2008; Kennedy et al., 2004; Lau et al., 2007). While novel PFASs have very similar stable structures, the corresponding potential toxicity studies are very limited. Short-chain PFASs are more likely than legacy long-chain PFASs to pass the placental barrier and accumulate in the fetus, raising concerns about PFAS exposure levels in fetuses and neonates who are highly vulnerable to potentially harmful environmental chemicals (Chang et al., 2021).

Food intake and drinking water are the main PFAS exposure routes in non-occupational populations (Poothong et al., 2020). Sociodemographic characteristics and living habits also affect the level of exposure to PFASs. Some evidence indicates that PFASs can be passed from mother to fetus through the placenta and have adverse effects on fetal growth and development, including low birth weight and reduced head circumference (Lee et al., 2016). Although maternal serum can be substituted for umbilical cord serum, the composition of PFASs may differ between the two matrices due to chemical-specific differences in delivery efficiency, suggesting that the relative exposure of PFASs to the fetus may be different from that of the mother, and, thus, the concentrations of PFASs in umbilical cord serum. Umbilical cord serum may be a more accurate reflection of fetal exposure than the maternal serum concentration.

Significant geographical differences in exposure levels have been reported for umbilical cord serum PFASs in different studies, and the factors affecting the exposure level also vary. Understanding the exposure levels and factors affecting umbilical cord serum PFAS concentrations would help prevent and control exposure to PFASs, thereby further reducing PFAS exposure and the potential health risks.

The purpose of this study was to obtain the exposure data of neonatal PFASs from umbilical cord serum samples and explore the potential determinants of fetal exposure. This study also provides a scientific basis for preventing and controlling PFAS exposure and reducing potential health risks.

2. Materials and methods

2.1. Sample collection

Pregnant women (n = 66) who were examined and delivered in a maternity hospital in Shijiazhuang, Hebei from January 2022 to March 2022 were selected as the research subjects. The subjects were all women who did not give birth to live fetuses with congenital malformations. Cord blood was collected for PFAS testing. In addition, the subjects completed a questionnaire on their own. The questionnaire asked about family income, education, occupation, dietary habits, smoking, drinking, and nutritional intake. The medical records were queried to determine the mother's age, pre-pregnancy weight, gestational weight, height, newborn gender, birth weight (g), birth length (cm), and other factors. The Ethics Committee of the Hebei Province Center for Disease Control & Prevention evaluated and approved this study protocol (IRB(S)2020–025).

2.2. Chemicals and materials

Details regarding the abbreviations and concentrations of all targeted compounds are provided in Table S1. Wellington Laboratories (Guelph, ON, Canada) provided the standards for the legacy and novel PFASs, including PFAC-MXB, MPFAC-MXA, and MFOSA (but not TFA or PFPrA). The two analytes (TFA and PFPrA) were purchased from the ANPEL (Shanghai, China). All standards were of the highest available purity (>98%). ThermoFisher Scientific Co. (Pittsburgh, PA, USA) supplied the fetal bovine serum (FBS). Solvents including ammonium hydroxide solution (NH_4OH, ≥25%, purity) were purchased from Yongda Reagent (Tianjin, China). Methanol (HPLC grade), ammonium acetate (HPLC grade), acetonitrile (HPLC grade), and acetic acid (glacial, Reagent Plus®, ≥99%) were obtained from Merck KGaA (Shanghai, China). Deionized water (HPLC grade) was Watson's distilled water. Oasis WAX solid phase extraction (SPE) cartridges were obtained from Waters (Shanghai, China).

PFASs are classified according to the length of the carbon chain into short-chain (C_2–C_6: TFA, PFPrA, PFBA, PFPeA, PFHxA, PFBS, PFHxS, and FHxSA), and long-chain (C_7–C_{18}: PFHpA, PFOS, PFDS, PFOA, PFNA, PFDA, PFUdA, PFDoDA, PFTeDA, PFTeDA, PFHxDA, and PFOcDA) groups. The full names of all compounds are listed in the Supporting Information (Table S1).

2.3. Sample pretreatment

After delivery, the cord blood was centrifuged at 3500 rpm for 10 min, and the serum was cryopreserved at −80 °C before being transported on dry ice to the laboratory at the Hebei Provincial Center for Disease Control and Prevention.

A 1 mL separated cord serum sample was spiked with 1 ng of the internal standard, and 2 mL of acetonitrile was added. The mixture was vortexed for 30 s before being recentrifuged for 10 min at 3500 rpm. The supernatant was collected and loaded onto an Oasis WAX SPE cartridge. The cartridges were preconditioned at a rate of one drop/s with 4 mL of 0.1% ammonium hydroxide (in methanol), 4 mL of methanol, and 4 mL of Milli-Q water. After loading the samples onto the cartridges, they were washed with 4 mL of 0.1% acetic acid. Then, 2 mL of MeOH was added to collect FHxSA, while 6 mL of 0.5% ammonium hydroxide was added to collect PFAAs (perfluoroalkylated acids) (in methanol). Both eluates were filtered through a 0.22 μm acetate membrane. The eluates were concentrated to near dryness (40 °C) under N_2 gas and reduced in 100 μL of methanol/aqueous ammonium acetate solution (v/v, 1:9). The eluates were transferred to an injection vial for further analysis.

2.4. Instrumental analysis

An ultra-high performance-tandem mass spectrometry system (Waters, ACQUITY UPLC TQ-S) system was used for the PFAS analysis. The flow rate was 0.3 mL/min, and the starting conditions were 90% of a 5

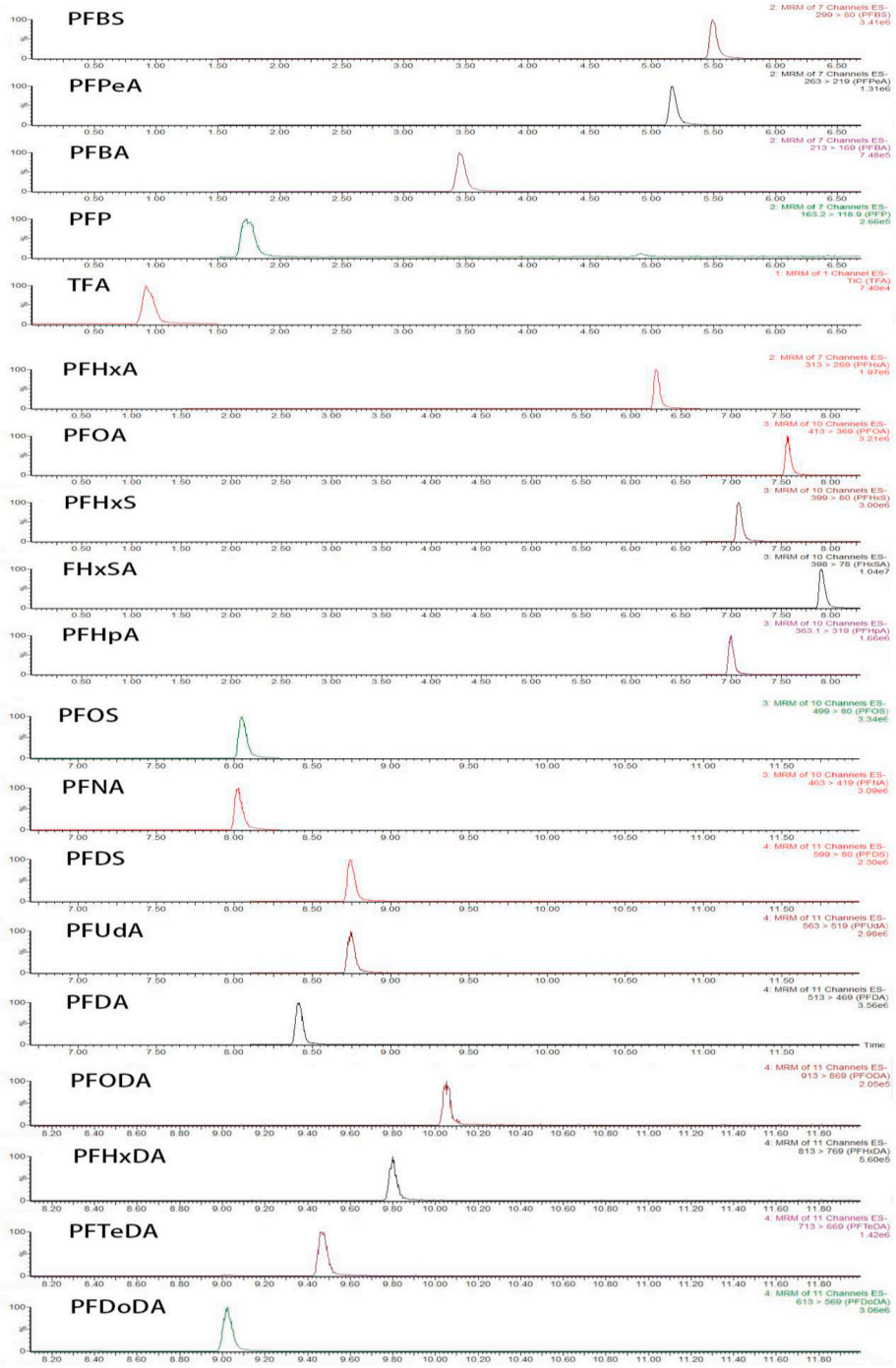

Fig. 1. Chromatogram of C2–C18 PFAS separation using Shield RP18 column.

mM aqueous solution of ammonium acetate (mobile phase A) and 10% MeOH (mobile phase B). The elution gradient was: 0 min (10% B), 10 min (98% B), 13 min (98% B), 14 min (10% B), and 16 min (10% B). The total run time was 16 min. The column temperature was 40 °C. Ten microliters of the sample were injected in this study.

The tandem mass spectrometer was operated in negative electrospray ionization mode. Scheduled multiple reaction monitoring algorithm mode was used to maximize instrument performance. The chromatogram is shown in Fig. 1. The source temperature was 100 °C, and the desolvation temperature was 350 °C. Nitrogen was used as the desolvation gas, at a flow rate of 900 L/h. Argon was used as the collision gas. The cone gas flow rate was 100 L/h, and the capillary voltage was 3 kV. Table S2 in the SI provides the parent and daughter ions of each analyte, as well as their corresponding collision energy, cone voltage, and the internal standard.

2.5. Quality assurance and quality control

The PFASs were quantified using the isotopic internal standard method. A program blank analysis using FBS was performed on each batch of samples to ascertain whether the contamination was introduced during the sequential extraction of serum from each batch of samples. All experimental equipment was rinsed with chromatographic-grade methanol at the same time.

The range of the calibration curve used to quantify the PFASs was 0.05–3.00 ng·mL^{-1} with r ≥ 0.997 (Table S3). The internal standard level was 1.00 ng·mL^{-1}. Cord serum samples were spiked to contain three concentrations of PFASs, such as high (2 ng·mL^{-1}), medium (0.5 ng·mL^{-1}), and low (0.2 ng·mL^{-1}, TFA:1ng·mL^{-1}) to determine recovery and precision. The recoveries of the PFASs ranged from 52.1% to 117.8%, and the RSD was <20%. The limits of detection (LOD) of the PFASs varied from 0.001 to 0.022 ng·mL^{-1} (Table S3). The LODs of the PFASs were determined at concentrations with a signal-to-noise ratio ≥3.

2.6. Statistical analysis

EpiData 3.1 was used for data entry and SPSS software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The concentrations and distributions of the 19 PFASs in cord serum are described using medians and interquartile ranges. When the concentration of PFASs was lower than the LOD, LOD/$\sqrt{2}$ was used. As the distribution of PFAS concentrations was skewed, we performed a natural logarithmic transformation to achieve an approximately normal distribution before performing the statistical analysis. Spearman's rank correlation analysis was used to detect the correlations between the PFASs and the content of each substance in cord serum. The Kruskal-Wallis test was used to analyze the distribution of PFASs in cord serum among the different influencing factors. A two-sided P-value <0.05 was considered significant.

3. Results and discussion

3.1. PFASs in cord serum

17 of the 19 analytes were found in the umbilical serum, and the presence of PFASs in the umbilical serum indicated that chemicals could cross the placental barrier. The detection rates of PFBS, PFBA, PFHpA, PFDA, PFDS, and FHxSA were low (2%, 5%, 21%, 1%, 12%, and 6%), while PFNA, PFOS, PFUdA, PFPrA, and PFHxS were detected at > 70%. PFOA had a 100% detection rate, whereas PFHxDA and PFO-cDA did not.

Concentrations of ∑PFASs ranged from 0.174 to 9.000 ng·mL^{-1} (median:2.745 ng·mL^{-1}). The concentration ranges of short-chain and long-chain PFASs were (0.000–7.714) ng·mL^{-1} and (0.117–3.990) ng·mL^{-1}. These data reflect that traditional long-chain PFASs are still the main contributors to human exposure to PFASs, while the significant increase in the concentrations of emerging short-chain alternatives cannot be ignored, as well as the potential health risks brought by the high concentration of long-chain PFASs. The recent manufacture and use of short-chain PFASs as alternatives to long-chain chemicals may be to blame for the decline.

Our findings provide evidence that the widespread use of PFAS alternatives and their exposure levels have increased quickly. Consistent with our results, other studies have reported that the novel PFASs are only slightly lower or even at the same level as the legacy PFASs (Duan et al., 2020; J et al., 2020; Wang et al., 2021).

As shown in Figs. 2 and 3, PFOS was the largest contributor to all target PFASs, accounting for 40.0% of the total PFAS concentration, with a concentration range of 0.225–3.629 ng·mL^{-1}. The next three biggest sources of PFAS concentration were PFPrA, PFPeA, and TFA, each of which contributed 21.4%, 14.9%, and 11.5% of the overall concentration, respectively. Concentrations of PFOS in subjects from the present study (Shijiazhuang, China) were consistently lower than those previously reported in subjects living in China, including cities such as Shanghai (2.48 ng mL^{-1}, the same below) (Wang et al., 2016), Wuhan (median: 3.64 ng·mL^{-1}) (F et al., 2017) and Guangzhou (3.00 ng·mL^{-1}) (Li et al., 2017). However, concentrations of PFOS in subjects from the present study are still higher than those in other countries (Kang et al., 2021; Richterová et al., 2018). Compared with PFOA, PFOS is produced in larger quantities in eastern China. PFOS is currently primarily used in metal plating as a chrome mist inhibitor. Notably, the metal plating industry is concentrated in eastern China, including Shijiazhuang, with extremely high regional emission intensity of PFOS (Wang et al., 2021). It is thought to play a significant role in the high level of PFOS in cord serum. Although PFOA emissions are lower, it is widely used and has multiple exposure routes. The country is gradually phasing out PFOS, and amount of PFOA used in households has improved. (Liu et al., 2017). The finding that PFOA was detected in all cord serum samples confirms this trend. In this study, the PFPeA concentration was much higher (0.04 ng·mL^{-1}) than in Beijing, China 2015–2016 (Gao et al., 2019). Few studies have been performed on PFPeA in cord blood, so determining its change in cord serum was impossible. However, PFPeA levels in adult serum are significantly higher (Chang et al., 2021). In this case, additional research is required.

TFA was detected in 55% of the cord serum samples at a concentration range of 0.006–2.476 ng·mL^{-1} (median: 0.229 ng·mL^{-1}). To the best of our knowledge, this is the first study to report the level of TFA in cord serum. TFA originates from a wide range of sources. TFA is used in the chemical industry and as a laboratory reagent and indirect sources of TFA are increasing, such as atmospheric oxidation of new refrigerants, photodegradation or thermal decomposition of fluoropolymers, and degradation of trifluoromethyl-containing drugs and plant protection agents, among others. These indirect sources may increase the release of TFA into the environment and lead to further human exposure. In addition to TFA, another short-chain substance, PFPrA, was widely detected in human serum at concentrations comparable to TFA. PFPrA can be generated in the atmosphere by the photodegradation of precursors of neutral PFASs (D'eon et al., 2006; Ellis et al., 2004; Martin et al., 2006).

3.2. Correlation with each component

Spearman's correlation analysis was performed on the PFASs with a detection rate >50% (excluding FHxSA). As shown in Table 1, the correlation between short and long-chain compounds was not significant (P > 0.05); however, there were differing degrees of correlations between various PFASs. The majority of PFASs were positively correlated, which may be related to the sources or routes of exposure (such as indoor dust from food or fluoropolymer degradation): PFPrA, PFOA, PFOS, PFNA, and PFUdA were significantly correlated with each other. TFA and PFPeA have a significant correlation. A positive correlation was detected between PFNA, PFOA, and PFOS, but not between PFOA and PFOS. The

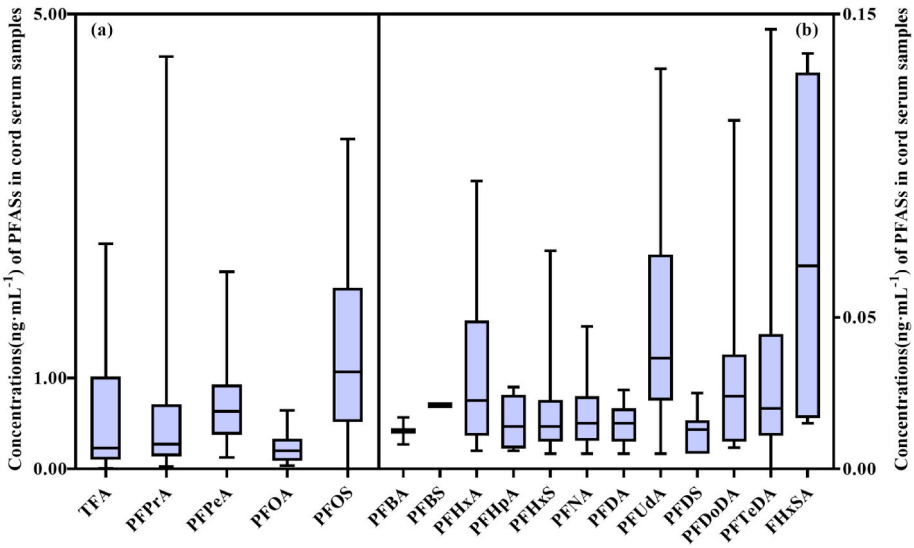

Fig. 2. PFAS concentrations in cord serum samples (n = 66). Boxes indicate the 25th, 50th and 75th percentiles, and whiskers indicate the 5th and 95th percentiles.

correlation coefficients ranged from 0.25 to 0.51, indicating a strong and positive correlation with PFOA ($r = 0.51$, $P < 0.0001$).

In an oxygen-enriched environment, many PFASs are degraded into perfluoroalkyl acids (PFAAs) (Mejia-Avendaño et al., 2016). Additionally, as organic intermediates, ultra-short-chain PFASs, such as TFA, can stimulate the synthesis of PFAAs. The negative correlation between TFA, PFPeA, and other PFASs supports this conclusion to some extent, with correlation coefficients ranging from −0.23 to −0.08 and from −0.25 to −0.10, respectively.

Similarly, FHxSA, an intermediate degradation product, is converted to PFAA under oxygen-enriched circumstances. The highest content of FHxSA in this investigation was 0.137 ng mL^{-1}, which was adversely linked with the majority of PFASs. The detection rate of FHxSA was low (correlation coefficients ranging from −0.25 to −0.01). This observation suggests that the blood environment operates as a site of FHxSA degradation and transformation. The association between chemicals is poor because there is insufficient oxygen in circulation and the conversion efficiency is low. FHxSA was only negatively correlated with PFOA ($r = -0.25$, $P < 0.05$), indicating that PFOA might be the final product of FHxSA conversion.

3.3. Factors related to the PFAS levels

We evaluated the univariate relationships between PFASs in cord plasma and each group of factors (Table 2). In general, no significant difference was observed in the ∑PFASs for each factor, but significant differences were detected between the different types of PFASs, including maternal education, age, frequency of nutrient supplementation during pregnancy, and eating habits during pregnancy.

The results showed that the higher the maternal education level, the more significant the association with significantly higher levels of various PFAS (PFHxS, PFOA, and PFDA). In this study, females with more education spent relatively longer time indoors, and indoor dust exposure is also an important way to be exposed to PFASs, so more PFASs accumulate in the body. Previous studies have shown that the levels of PFASs in older pregnant women are also higher, and this study confirmed this finding, as the concentrations of PFDA were significantly different between the age groups, and the older the age, the higher the concentration. The PFDA concentrations increased with increasing maternal age, which may be due to the time accumulating effect of PFASs, and their long biological half-life. However, some studies have suggested that PFASs bind to serum albumin, which decreases with age and may be why some PFASs do not increase with age (Weaving et al., 2016). Thus, larger population studies are required to confirm the effect of age on PFASs.

The dietary structure can affect PFAS exposure, as fish appear to be a major factor in food exposure to PFASs (Wang et al., 2021). Studies have shown that the serum levels of PFOS in people who consume large amounts of fish are nearly three times higher than those in a control group (Richterová et al., 2018). The results of this study also showed that the concentrations of most PFASs and ∑PFASs in the cord serum of pregnant women who ingested more marine fish were higher and all of the PFASs trended up. Similarly, increased consumption of milk, wheat, and nuts may reduce PFASs levels in the body. Some studies have reported high levels of PFASs in eggs, but no effect of eggs on the concentration of PFASs was found in this study. In general, pregnant women should increase their intake of milk, nuts, and wheat, and reduce their intake of marine fish, thereby reducing the intrauterine exposure level of PFASs during pregnancy.

This study discovered that nutrient supplementation during pregnancy affected PFAS concentrations and that their concentration levels (PFHxS, PFDA, PFUdA, PFDS) decreased with increasing frequency of nutrient supplementation, suggesting that nutrients may inhibit PFAS accumulation. Pregnant women supplemented with calcium regularly had a nearly 20-fold (0.0010–0.0195 ng·mL^{-1}) reduction in serum PFDS concentrations compared to those who were never supplemented during pregnancy. Because PFASs are proteolytic compounds, calcium supplementation inhibits PFAS binding to serum proteins, resulting in lower loading levels (Xia et al., 2015).

Docosahexaenoic acid (DHA) promotes the development of brain volume in the fetus after birth. PFAS, which has a structure similar to DHA, has the opposite effect on brain development (Lefkowitz, 1975). Lower median concentrations of PFHxS, PFDA, and PFDS were detected in the cord sera of people who regularly supplemented with DHA compared to those who never took DHA. These substances compete with the corresponding receptors and become antagonistic, so the increase in DHA levels affects the decrease in the level of PFASs.

The folate concentration in the body is also related to the level of exposure to PFASs. A recent study reported that an increase in the concentrations of selected PFAAs results in a decrease in the concentration of folate in blood cells, and the degree of the decrease depends on the carbon chain length of the PFAS (Jain, 2021). In other words, the higher the concentration of folate in blood cells, the lower the concentration of PFASs; the longer the carbon chain, the faster the folate concentration declines. The mechanism of action is unknown, but this phenomenon was also observed in this study with the PFASs ($C < 8$). The

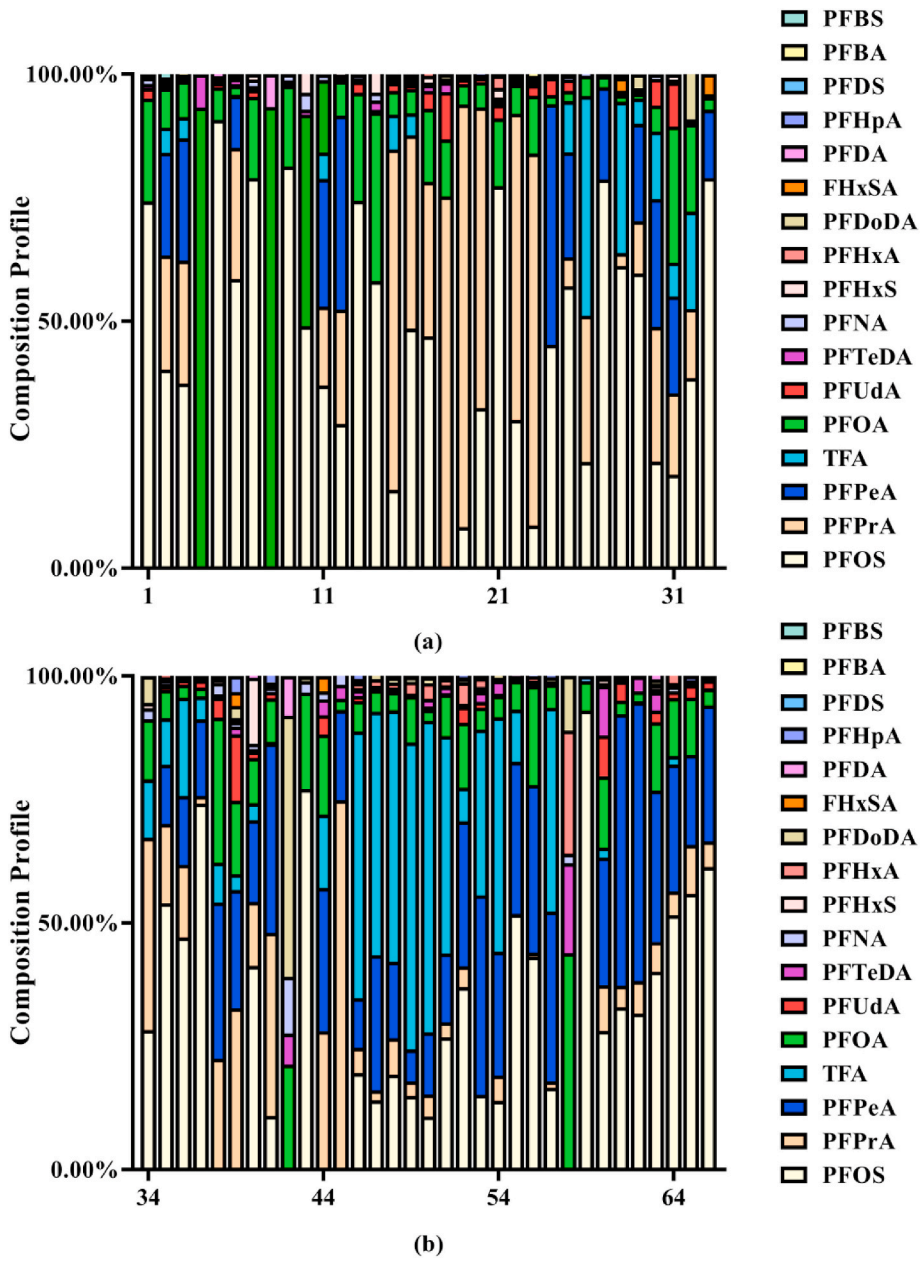

Fig. 3. Composition of PFASs in cord serum.

Table 1
Spearman correlation coefficients among serum PFAS concentrations.

	Short-chain				Long- chain					Precursor
	TFA	PFPrA	PFPeA	PFHxS	PFOA	PFOS	PFNA	PFUdA	PFTeDA	FHxSA
TFA	1.00									
PFPrA	0.23	1.00								
PFPeA	0.29*	0.07	1.00							
PFHxS	−0.15	0.25*	−0.14	1.00						
PFOA	−0.23	0.01	−0.25*	0.51**	1.00					
PFOS	−0.08	−0.02	0.18	0.29*	0.13	1.00				
PFNA	−0.14	0.31*	−0.10	0.45**	0.31*	0.26*	1.00			
PFUdA	−0.10	0.27*	0.02	0.46**	0.18	0.14	0.10	1.00		
PFTeDA	−0.08	−0.01	−0.16	0.14	0.03	−0.12	0.01	0.08	1.00	
FHxSA	0.06	−0.08	−0.10	−0.09	−0.25*	−0.01	−0.16	0.01	−0.10	1.00
Short-chain	1.00				0.17					−0.11
Long-chain	0.17				1.00					−0.03

* P-value < 0.05.
** P-value < 0.01.

Table 2
Concentrations (ng·mL^{-1}) of PFASs in cord serum as stratified by sociodemographic characteristics.

Characteristics		Median Concentrations						
		∑PFASs	PFPeA	PFHxS	PFOA	PFDA	PFUdA	PFDS
Maternal education	Primary	0.3440	–	0.0015	0.0370	0.0040	0.0030	–
	Middle	3.2403	0.4300	0.0023	0.1605	–	0.0145	–
	High and Technical School	2.7868	0.6765	0.0018	0.1585	–	0.0215	–
	Undergraduate degree	2.7040	–	0.0125	0.2070	–	0.0355	–
	Graduate and above	3.1175	–	0.0180*	0.2870*	0.0170*	0.0360	–
Maternal age (year)	< 25	3.2585	0.3710	–	0.3660	–	0.0250	–
	25–35	2.6640	0.3390	0.0045	0.1835	–	0.0230	–
	35–40	4.6928	0.0040	0.0025	0.3030	0.0125*	0.0330	–
	> 40	2.2450	0.3820	–	0.0710	–	0.0470	–
Nutrients supplementation	Calcium							
	Never	3.9343	0.0040	0.0023	0.1045	0.0100	0.0150	0.0195*
	Sometimes (≤4times/week)	3.7560	0.4300	0.0100	0.1850	–	0.0340	0.0050
	Regularly (≥4times/week)	2.8925	0.3680	0.0050	0.2390	–	0.0240	0.0010
	DHA							
	Never	3.0230	0.4510	0.0300	0.1850	0.0500	0.0210	0.0100*
	Sometimes (≤4times/week)	3.2585	0.0040	0.0200*	0.2380	0.0270	0.0340	0.0040
	Regularly (≥4times/week)	2.1998	0.0650	0.0090	0.2720	0.0050*	0.0260	–
	Folic acid							
	Never	4.8335	0.8270	0.0110	0.1710	–	0.0860*	–
	Sometimes (≤4times/week)	2.6948	0.2065	–	0.2625	–	0.0525	–
	Regularly (≥4times/week)	2.9150	0.3695	0.0050	0.1995	–	0.0195	–
	Probiotics							–
	Never	2.9803	0.3460	0.0045	0.1835	–	0.0240	–
	Sometimes (≤4times/week)	2.4168	0.5915	–	0.2545	–	0.0475	–
	Regularly (≥4times/week)	4.8735	0.0040	0.0113	0.3705	0.0260*	0.0470	–
Foods intake	Milk							
	Never	3.0578	0.6765*	0.0080	0.1675	–	0.0155	–
	Sometimes (≤4times/week)	3.3255	0.5070	0.0070	0.1550	–	0.0260	–
	Regularly (≥4times/week)	2.6470	0.2580	0.0050	0.2570	–	0.0240	–
	Sea fishes							
	Never	2.2250	0.3608	0.0117	0.2575	0.0052	0.0110	0.0036
	Sometimes (≤4times/week)	2.9848	0.3460	0.0055	0.1835	–	0.0275	–
	Regularly (≥4times/week)	3.8100	0.4920	0.0030	0.2660	–	0.0358*	–
	Eggs					–		–
	Never	4.0595	0.0040	0.0435	0.4785	–	0.0260	–
	Sometimes (≤4times/week)	2.6185	0.5480	0.0060	0.1435	–	0.0335	–
	Regularly (≥4times/week)	2.9150	0.3695	0.0050	0.2005	–	0.0240	–
	Wheats							–
	Never	6.5815	–	0.0360*	0.3750	0.0090	0.0490	–
	Sometimes (≤4times/week)	2.7610	–	0.0180	0.2380	0.0050*	0.0360	–
	Regularly (≥4times/week)	2.9150	0.3720	0.0045	0.1860	–	0.0240	–
	Nuts							
	Never	3.3985	0.5345	0.0080	0.3135	0.0065	0.0365	0.0025
	Sometimes (≤4times/week)	2.9375	0.3390	0.0090*	0.1885	–	0.0240	–
	Regularly (≥4times/week)	2.6640	0.3565	0.0030	0.2125	–	0.0310	–

* Statistically significant differences ($p < 0.05$) using Mann–Whitney *U* test or Kruskal–Wallis test.
—Not listed because of a value below the LOD.

decrease in the concentration among the groups was not obvious or even increased, whereas the decrease in the PFASs (C ≥ 8), such as PFUdA, was significant. In addition, animal experiments show that probiotics alleviate the toxic damage caused by PFOS to a certain extent, but the effect on exposure levels is unknown (Sun et al., 2020).

Although factors, such as pregnancy body mass index (BMI), maternal occupation, drinking water source, and other factors did not statistically affect the differences in the PFASs, relative trends in the concentrations among the different groups were observed. Compared with the normal range of BMI during pregnancy (18.5–30 kg/m^2), the concentration of PFASs in groups with too high or too low of a BMI increased; the concentration of PFASs in groups of related occupations that were prone to PFAS exposure was higher than that in non-such occupational groups. The group who drank bottled water had lower PFAS concentrations than those who drank tap water, public tap water, or well water.

3.4. Neonatal birth weight and PFASs

Birth weight is an important parameter for assessing infant health because it is linked to the risk of infant and child mortality, coronary heart disease, and other health problems. All 66 neonates were singleton live births, including 5 preterm infants, and all of their growth indices were within the normal range. The average birth weight of the newborns was 3216.39 ± 562.98 g, the average length was 50.00 cm, and the average head circumference was 31.05 cm.

In this study, among the two types of long-chain and short-chain PFASs, long-chain PFASs were associated with neonatal birth weight ($r = -0.303$, $P < 0.05$), and a significant negative correlation was detected between neonatal birth weight and PFOS ($r = -0.319$, $P < 0.05$), indicating that an increase in the PFOS concentration will lead to an increase in the probability of low neonatal birth weight, which is consistent with previous results (Kang et al., 2021). The birth weights of

newborns were divided into groups: low birth weight (<2500 g), average (2500–4000 g), and overweight (>4000 g), and the relationship between them and the concentrations of PFASs was tested non-parametrically. Significant differences were detected between the groups, with a higher concentration of PFDoDA in the low birth weight group (median: 0.012 ng·mL^{-1}), which was twice as high as in the other two groups; PFUdA increased more in the normal body weight group than in the other two groups (median: 0.034 ng·mL^{-1}).

Many studies on the relationship between birth weight and PFAS concentrations in umbilical cord blood have reported that the relationship between PFAS exposure and birth weight is affected by the research design, sample size, and demographic characteristics, resulting in inconsistent relationships. The big reason for this is that few studies have investigated the reproductive and developmental toxicity of other PFOSs besides PFOS and PFOA (Lee et al., 2016). One of the reasons why PFOS and PFOA affect birth weight is that they affect the level of circulating PFASs through hemodynamic or physiological changes as presented by physiological-based pharmacokinetic models, thereby affecting birth weight (Loccisano et al., 2012; Whitworth et al., 2012).

This study has some limitations. First, our study is a cross-sectional study, and the results only reflect PFAS exposure in cord serum at this time. However, the evolution of PFAS exposure *in utero* through newborns and children has not been tracked over time. Second, the concentration of PFASs in cord serum only indicate the fetus's internal exposure. Less is known about the exposure paths and sources. Finally, this study's sample size is tiny, and some data are missing. So it is necessary to expand the sample size and conduct long-term observations and investigations on the future development and growth of infants and young children, to generate more accurate results.

4. Conclusions

The purpose of this study was to provide a basis for subsequent assessments of neonatal PFAS exposure risk by focusing on intrauterine exposure levels and the impact of potential factors on intrauterine exposure and neonatal birth weight. The present study demonstrated that legacy PFASs remain the major contributors to the composition of human PFASs, but the levels of emerging short-chain alternatives have increased significantly, which cannot be ignored. The concentrations of TFA and PFPrA in human cord serum were also reported in our study for the first time. Furthermore, several maternal characteristics, including maternal age, education, nutritional supplements, and diet during pregnancy affect PFAS exposure differently.

Credit author statement

Jingwen Jia: Conceptualization, Methodology, Writing – original draft. **Lihong Duan:** Investigation. **Bingqi Dong:** Methodology, Validation, Formal analysis. **Qiuying Dong:** Formal analysis. **Wanqin Yu:** Formal analysis, Methodology. **Yinping Liu:** Methodology. **Lixin Yang** Visualization, Writing – review & editing, Resources, Project administration. **Hongmei Shi:** Writing – review & editing, Project administration.

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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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