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Adverse birth outcomes related to concentrations of per- and polyfluoroalkyl substances (PFAS) in maternal blood collected from pregnant women in 1960–1966

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ABSTRACT

Background: Prior animal and epidemiological studies suggest that per- and polyfluoroalkyl substances (PFAS) exposure may be associated with reduced birth weight. However, results from prior studies evaluated a relatively small set of PFAS.

Objectives: Determine associations of gestational PFAS concentrations in maternal serum samples banked for 60 years with birth outcomes.

Methods: We used data from 97 pregnant women from Boston and Providence that enrolled in the Collaborative Perinatal Project (CPP) study (1960–1966). We quantified concentrations of 27 PFAS in maternal serum in pregnancy and measured infant weight, height and ponderal index at birth. Covariate-adjusted associations between 11 PFAS concentrations (>75% detection limits) and birth outcomes were estimated using linear regression methods.

Results: Median concentrations of PFOA, PFNA, PFHxS, and PFOS were 6.189, 0.330, 14.432, and 38.170 ng/mL, respectively. We found that elevated PFAS concentrations during pregnancy were significantly associated with lower birth weight and ponderal index at birth, but no significant associations were found with birth length. Specifically, infants born to women with PFAS concentrations ≥ median levels had significantly lower birth weight (PFOS: $\beta = -0.323$, $P = 0.006$; PFHxS: $\beta = -0.292$, $P = 0.015$; PFOA: $\beta = -0.233$, $P = 0.03$; PFHpS: $\beta = -0.239$, $P = 0.023$; PFNA: $\beta = -0.239$, $P = 0.017$). Similarly, women with PFAS concentrations ≥ median levels had significantly lower ponderal index (PFHxS: $\beta = -0.168$, $P = 0.020$; PFHxA: $\beta = -0.148$, $P = 0.018$).

Conclusions: Using data from this US-based cohort study, we found that 1) maternal PFAS levels from the 1960s exceeded values in contemporaneous populations and 2) that gestational concentrations of certain PFAS were associated with lower birth weight and infant ponderal index. Additional studies with larger sample size are needed to further examine the associations of gestational exposure to individual PFAS and their mixtures with adverse birth outcomes.

1. Introduction

Epidemiologic studies have shown that adverse birth outcomes (such as low or high birth weight and preterm birth) are associated with an increased risk of diseases in both children and adulthood, including obesity, hypertension, cardiovascular diseases, diabetes, and cancers (Drozdz et al., 2021; Wang et al., 2022; World Cancer Research Fund International). Thus, identification of the risk factors for adverse birth

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outcomes will help to improve children's health and inform prevention strategies for many adult diseases.

There has been increasing interest in determining if prenatal exposure to per- and polyfluoroalkyl substances (PFAS) increases the risk of adverse birth outcomes (Sagiv et al., 2018; Shoaff et al., 2018; Kato et al., 2014; Stein et al., 2009; Louis et al., 2016; Darrow et al., 2013; Starling et al., 2017; Eick et al., 2020; Marks et al., 2019; Maisonet et al., 2012; Whitworth et al., 2012; Washino et al., 2009; Kwon et al., 2016; Hamma et al., 2010; Wu et al., 2012; Ashley-Martin et al., 2017; Callan et al., 2016; Bach et al., 2016; Liu et al., 2020; Souza et al., 2020; Jensen et al., 2015; Lee et al., 2013; Huo et al., 2020; Wang et al., 2019). Experimental studies demonstrate that *in utero* exposure to PFAS reduces fetal growth and birth weight in animals (Lam et al., 2014; Koustas et al., 2014). Two recent meta-analyses of the epidemiologic literature have reached conflicting conclusions. Gao et al. (2021) concluded that PFAS exposure during pregnancy is largely unassociated with low birth weight (LBW) and small for gestational age (SGA) but that there is a linear (PFOS) or nonlinear (PFOA and PFNA) increase in pre-term birth risk. On the other hand, Gui et al. (2022) reported that several major PFAS (PFOS, PFOA, PFHxS, PFNA, PFUnDA, PFHpS, and PFDA) exposures were significantly associated with an increased risk of low birth weight, with effect sizes ranging from −181.2 g (95% confidence interval (CI) = −360.6 to −1.8) per 1 ng/mL increase in PFHpS, to −24.2 g (95% CI = −38.64 to −9.9) per 1 ln (ng/mL) increase in PFDA. These investigators have stressed the need for further study of the relationship between PFAS exposure and birth outcomes in additional, independent cohorts.

PFAS was synthesized in the US in the 1930s, and introduced to the market in the 1940s with increasing use in the US in the 1950s. (United States Environmental Protection Agency) Furthermore, we are unaware of any study to date that has explored the association between PFAS and adverse birth outcomes from exposures occurring during the years immediately following widespread use in consumer and industrial products in the 1950s and 1960s.

The US Collaborative Perinatal Project (CPP) (Klebanoff, 2009; Buka et al., 2013) was a landmark NIH project that enrolled a large sample of pregnant women across the nation, upon registration at their hospital obstetrics clinic, from 1960 to 1966. Women provided non-fasting blood samples throughout pregnancy and at delivery; serum was stored in glass at −20 °C, and information on pregnancy and birth outcomes was systematically gathered. This invaluable resource provides us a unique opportunity to assess both PFAS levels during pregnancy, as well as the potential association with adverse birth outcomes in a time period with a rapid increase in PFAS use. In this study, we used the blood samples collected at birth from 97 pregnant women of the New England-CPP cohort (NE-CPP), stratified by year of recruitment, to explore whether prenatal exposure to PFAS in these cohort participants was associated with adverse birth outcomes.

2. Methods

2.1. Study participants

The US CPP included fourteen university-affiliated medical centers throughout the United States (Klebanoff, 2009; Buka et al., 2013). The NE-CPP included two CPP enrollment sites in New England: Providence, RI (~4000 pregnancies enrolled) and Boston, MA (~13,000 pregnancies were enrolled). More than 98% of the cohort have pregnancy and birth outcome data, including birthweight and birth length. Information on demographic variables and medical and pregnancy history of the pregnant women is also available. From these women of NE-CPP that have both birth outcome information and stored blood samples, we selected 97 women for this pilot study, stratifying by years of recruitment (n = 28 for 1960-61; n = 38 for 1962-63; and n = 31 for 1964-66). The sample included 27 offspring who showed signs of metabolic syndrome in adulthood. A second banked sample from the same draw date was selected for a random five participants to examine consistency of assay results (see Appendix 2).

2.2. Laboratory analyses of PFAS

Samples were prepared using isotope dilution analysis. Briefly, a solution containing 13 isotopically labeled PFAS internal standards (Wellington, Overland Park, KS) was prepared in LC-MS grade acetonitrile. The serum samples (300 μL) were spiked with 100 μL of the internal standard solution and 200 μL LC-MS grade acetonitrile, sonicated for 30 min, refrigerated at 4 °C overnight, and then centrifuged at 3000 rpm for 10 min. The supernatant was transferred to a LC-MS vial with a 350 μL insert for analysis. Targeted analysis of 27 PFAS were performed using a Thermo Vanquish Ultra High-Performance Liquid Chromatography (UHPLC) Orbitrap Q Exactive HF-X mass spectrometer (MS) following the chromatography conditions described in EPA Draft Method 1633 (Draft, 2021). Additional details of the analytical methodology are provided in the SI. The analytical standards (Wellington, Overland Park, KS) used for quantitation were prepared by serial dilution in 1:1 LC-MS grade water: acetonitrile containing 1 mM ammonium acetate and 0.1% formic acid. Concentrations of the standards ranged from 0.05 to 100 ng/mL. The limits of detection (LODs) ranged between 0.028 and 0.103 ng/mL. LODs were determined from seven injections of calibration standards and the equation: $LOD = [s \times t\ (df, 1 - \alpha = 0.99)]/m$ where s is the standard deviation, t is the student's t-value, df is the degree of freedom, α is the significance level ($n = 7$, $\alpha = 0.01$, $t = 3.14$), and m is the slope of the calibration curve (Armbruster et al., 2008; Long et al., 1983).

Samples were extracted and analyzed batches of 40 samples in a random sequence. Along with the study samples, each batch included a calibration curve, quality control (QC) materials, and reagent blanks to assure the accuracy and reliability of the data. Three QC materials were used including: (1) extraction blanks, which were charcoal striped fetal bovine serum (FBS), (2) recovery spikes, which were FBS spiked with a known concentration of PFAS, and (3) NIST Standard reference material (SRM) 1958. QC data are presented in SI Tables 2 and 3 Finally, for 5 participants, we selected and blindly assayed a second aliquot collected on the same date and stored since the 1960s, to assess the consistency of assay results across samples for the same participant.

2.3. Statistical methods

Multiple linear regression models were used to assess the associations between PFAS exposures at pregnancy and adverse birth outcomes for the PFAS that have serum concentration above the detection limits (more than 75% of the samples). In categorical analyses, women were classified into high (greater than or equal to the Median levels) or low (less than the median levels) exposure to each of the measured PFAS, and the low exposure group was used as reference category in regression models. Adjusted restricted cubic spline analyses were employed to assess potential non-linear associations between birth weight and maternal serum levels of five PFAS (PFOS, PFOA, PFHxS, PFHsP and PFNA) that the modeling results showed a significant negative association with maternal PFAS exposure. Models were adjusted for maternal age at pregnancy (years); weight change in pounds during pregnancy (lbs); duration of gestation in days (determined by earliest ultrasound or the date of last menstrual period); number of cigarettes smoked per day during pregnancy (none, <1 pack/day, and ≥1 pack/day), marital status (married vs other), parity (0 or 1); race (white vs other); family socioeconomic index (in tertiles); child sex and year of blood collection (1960-61, 1962-63, and 1964-66). Infant Ponderal index was calculated based on 100*Birth Weight (grams)/Birth Length (World Cancer Research Fund International) (cm).

In sensitivity analyses, we explored whether associations between PFAS and birth weight varied by child sex of the children since some studies have shown sexually-dimorphic associations (Wikström et al., 2020). All statistical analyses were performed using the SAS version 9.4

(SAS Institute Inc. Cary, NC, USA).

3. Results

Table 1 shows selected demographic characteristics of the study population. The women had a mean age of 22.7 yrs at pregnancy and had a mean weight increase of almost 23 lbs during pregnancy. Thirty-seven percent of the women did not smoke. Among the smokers, 33% were heavy smokers (≥1pack/day). Seventy-one percent of the women were married at the time of pregnancy and for 54% of the women, this was their first pregnancy.

Table 2 shows the means, geometric means, medians, and selected percentiles for the 27 PFAS measured in the study serum samples. All 27 targeted PFAS had serum concentrations above the detection limits in at least 1 sample. Of these 27 PFAS measured, 4 (PFOS, PFHxS, PFOA and PFHpS) had serum concentrations above the detection limits in 99% of the samples; 11 had concentrations above detection limits in >75% of the samples while 14 were detectable for >50% of the samples. PFOS had the highest serum concentrations (median 38.170 ng/mL, interquartile range (IQR 22.497–75.089); followed by PFHxS (median 14.432 ng/mL, IQR 7.770–24.452); and PFOA (median 6.189, IQR 4.341–10.016). Table 3 shows the serum concentrations by year of blood collection, where 100% of the samples had serum concentrations above the detection limits for PFOS, PFOA, and PFHxS during 1962-63, and 1964-66. Compared to 1960-61, there was an almost 3-fold increase in serum levels of these three PFAS in 1962-63. PFOA and PFHxS had the highest serum levels during the final years of blood collection (1964-66).

Table 1
Demographic characteristics of the study pregnant women by sex of their children.

Variables	All N = 97	Boys N = 42	Girls N = 55
Age at pregnancy			
Mean ± SD	22.7 ± 5.6	23.1 ± 5.1	22.3 ± 6.0
Weight change during pregnancy (lbs)			
Mean ± SD	22.7 ± 10.5	22.3 ± 8.8	23.1 ± 11.7
Race			
White	62(63.9)	29(69.0)	33(60.0)
Other	35(36.1)	13(31.0)	22(40.0)
Marital status n (%)			
Single	20 (20.6)	5(11.9)	15(27.3)
Married	69 (71.1)	31(73.8)	38(69.1)
Other	8 (8.3)	6(14.3)	2(3.6)
# of smoking/day n (%)			
None	36 (37.1)	18(42.9)	18(32.7)
<1 pack	29 (29.9)	10(23.8)	19(34.6)
≥1packs	32 (33.0)	14(33.3)	18(32.7)
Prior pregnancy n (%)			
No	52 (53.6)	23(54.8)	29(52.7)
Yes	45 (46.4)	19(45.2)	26(47.3)
Sex of child n (%)			
Male	42 (43.3)	–	–
Female	55 (56.7)	–	–
Year of blood collection n (%)			
1960–1961	28(28.9)	12(28.6)	16(29.1)
1962–1963	38(39.2)	19(45.2)	19(34.5)
1964–1966	31(31.9)	11(26.2)	20(36.4)
Offspring metabolic syndrome at adulthood			
No	71(73.2)	30(61.4)	41(74.5)
Yes	26(26.8)	12(28.6)	14(25.5)
Gestation week at delivery			
Mean ± SD	40.3 ± 2.3	40.7 ± 2.4	39.9 ± 2.3
Birth Weight (kgs)			
Mean ± SD	3.2 ± 0.5	3.5 ± 0.4	3.1 ± 0.5
Birth Height (cm)			
Mean ± SD	50.3 ± 2.5	51.2 ± 2.3	49.7 ± 2.4
Infant Ponderal Index at birth (g/cm^3)			
Mean ± SD	2.5 ± 0.3	2.6 ± 0.3	2.5 ± 0.2
Socioeconomic index			
Mean ± SD	45 ± 19	51 ± 18	41 ± 18

For the 11 PFAS that had concentrations above the detection limits in more than 75% of the samples, we used both univariate and multivariate linear regression models to assess the association between serum PFAS levels and birth outcomes (Table 4). The results show a generally negative association between maternal serum PFAS levels during pregnancy and birth weight, birth length, and Ponderal Index. Relative to women whose serum levels are below the median, women whose serum levels ≥ Median had significantly lower birth weight for PFOS: β = −0.323, P = 0.006; PFHxS: β = −0.292, P = 0.015; PFOA: β = −0.233, P = 0.03; PFHpS: β = −0.239, P = 0.023; PFNA: β = −0.239, P = 0.017. A significant negative association was also observed between infant Ponderal Index with maternal serum levels of PFHxS: β = −0.168, P = 0.02; PFHxA: β = −0.148, P = 0.018. A ln-unit increase in maternal serum concentrations of five common PFAS (PFOS, PFOA, PFHxS, PFNA and PFHpS) also had a negative association with birth weight in adjusted analyses, but none of the associations was statistically significant (Table 5). A significant negative association, however, was observed between infant Ponderal Index with maternal serum levels of PFOS: β = −0.142, P = 0.045; PFHxS: β = −0.153, P = 0.024; and PFHxA: β = −0.135, P = 0.020 in adjusted analyses.

The adjusted restricted cubic spline analyses are presented in Fig. 1. We assessed potential non-linear associations between maternal serum levels of five major PFAS (PFOS, PFOA, PFHxS, PFHpS, and PFNA) and birth weight that the modeling results showed a significant negative association with maternal PFAS exposure. The spline analyses showed a significant negative linear association between maternal serum levels of PFOS and birth weight for PFOS exposure levels until ~50 ng/mL (Fig. 1a). This suggests, for example, that pregnant women who had a serum level of 50 ng/mL for PFOS would give birth to babies with about 354 g lighter than women who had the lowest serum levels of PFOS observed in this study. A significant negative linear association was also observed between PFOA and birth weight for PFOA exposure levels up until ~6.5 ng/mL (Fig. 1b). In this case, pregnant women who had a serum level of 5 ng/mL for PFOA, for example, would give birth to babies about 460 g lighter than women who had the lowest serum levels of PFOA in this study. Finally, a significant linear negative association was also observed for PFNA and birth weight until about 0.800 ng/mL (Fig. 1e).

In sensitivity analyses, we stratified the study pregnant women into two groups based on the sex of their children. As shown in Supplementary Table 1, among women who gave birth to girls, higher serum levels of PFHxS, PFHpS, and 8:2-FTS were associated with a significant negative association with infant Ponderal Index at birth. Among these women whose serum levels ≥ median, a significant decrease in the Ponderal Index was observed for PFHxS (β = −0.232, p 0.005), PFHpS (β = −0.179, p 0.001), and 8:2-FTS (β = −0.195, p 0.028), relative to women whose serum levels below the median. No similar associations were found among women who gave birth to boys while PFHxA (β = −0.310, p 0.024), among these women was associated with a significant decrease in birth weight Ponderal Index.

Among the five participants with a 2nd aliquot, we observed good reproducibility of PFAS concentrations across repeated samples. Among the 11 PFAS detected in >75% of serum samples, absolute differences in concentrations tended to be small in most cases and were greatest for PFOS and PFHxS in two participants (numbers 4 and 5), who had higher concentrations of these PFAS. However, relative differences were <16.4%. Additionally, relative differences among other participants and PFAS were generally <10% and in cases where it was higher, the absolute differences were small.

4. Discussion

In this pilot study, we found detectable serum levels of PFOS, PFHxS, PFOA and PFHpS in almost all blood serum samples collected from pregnant women by the NE-CPP cohort study in 1960-66. We also found that the infants of women who had higher serum levels of PFOS, PFHxS,

Table 2
Maternal serum levels of PFAS (ng/mL) during pregnancy, their levels of detection limits, and proportion above the detection limits.

PFAS	LOD(ppb)	Above LOD(%)	Machine Readable(%)	Mean	Geometrics Mean	Max	Median	P5	P25	P75	P95
PFOS	0.068	98.97%	98.97%	50.518	36.021	147.621	38.170	6.182	22.497	75.089	131.732
PFHxS	0.041	98.97%	98.97%	18.389	12.325	92.540	14.432	0.858	7.770	24.452	51.628
PFOA	0.041	98.97%	98.97%	7.291	6.280	19.158	6.189	2.411	4.341	10.016	14.148
PFHpS	0.039	98.97%	98.97%	1.185	0.779	6.890	0.936	0.088	0.434	1.460	3.440
PFNA	0.033	96.91%	100.00%	0.455	0.291	2.565	0.303	0.035	0.181	0.513	1.686
NMeFOSAA	0.069	94.85%	98.97%	1.032	0.560	8.901	0.641	0.069	0.272	1.202	3.615
PFPeS	0.028	93.81%	100.00%	0.448	0.209	10.391	0.221	0.020	0.126	0.446	0.974
NEtFOSAA	0.05	93.81%	97.94%	0.881	0.490	3.671	0.570	0.076	0.246	1.163	3.093
8:2-FTS	0.038	85.57%	86.60%	2.150	1.556	7.625	2.094	0.413	0.957	2.806	5.301
PFPeA	0.034	79.38%	91.75%	0.738	0.167	20.125	0.155	0.015	0.081	0.369	2.386
PFHxA	0.047	77.32%	98.97%	0.230	0.112	2.368	0.136	0.013	0.059	0.227	0.778
PFNS	0.053	55.67%	96.91%	0.178	0.075	1.618	0.078	0.008	0.023	0.228	0.575
PFDS	0.067	53.61%	81.44%	0.250	0.110	1.751	0.153	0.006	0.048	0.331	0.769
4:2-FTS	0.072	51.55%	53.61%	2.975	0.858	30.613	0.911	0.090	0.225	2.231	22.005
PFBS	0.063	42.27%	91.75%	0.150	0.045	3.183	0.056	0.003	0.025	0.093	0.435
PFDA	0.068	36.08%	49.48%	0.297	0.128	2.550	0.173	0.008	0.051	0.289	1.275
PFBA	0.041	28.87%	29.90%	0.283	0.173	1.895	0.131	0.055	0.101	0.288	0.793
PFHpA	0.036	15.46%	64.95%	0.054	0.009	0.596	0.008	0.001	0.002	0.031	0.416
PFTrDA	0.044	11.34%	47.42%	0.082	0.011	1.515	0.008	0.001	0.003	0.043	0.253
PFDoA	0.091	9.28%	24.74%	0.191	0.022	1.928	0.014	0.001	0.002	0.168	0.986
PFUdA	0.084	8.25%	24.74%	0.220	0.026	2.015	0.025	0.001	0.003	0.162	1.236
PFTeDA	0.072	8.25%	40.21%	0.076	0.011	1.415	0.008	0.001	0.003	0.030	0.576
PFODA	0.091	5.15%	62.89%	0.043	0.010	0.716	0.008	0.001	0.003	0.033	0.126
PFDoS	0.103	4.12%	44.33%	0.071	0.008	1.166	0.005	0.001	0.003	0.021	0.313
PFHxDA	0.085	6.19%	44.33%	0.049	0.007	0.773	0.006	0.001	0.001	0.018	0.248
NMeFOSA	0.029	2.06%	9.28%	0.065	0.015	0.312	0.011	0.001	0.005	0.025	0.312
FOSA	0.038	1.03%	41.24%	0.030	0.005	0.921	0.006	0.001	0.001	0.010	0.022

Table 3
Maternal serum levels of major PFAS (ng/mL) during pregnancy by year of blood collection.

PFAS	Year Group	LOD (ppb)	Above LOD (%)	Machine Readable(%)	Mean	Geometrics Mean	Max	Median	P5	P25	P75	P95
PFOS	1960–1961 (N = 28)	0.068	96.43%	96.43%	27.615	18.946	147.621	25.743	1.830	14.550	30.417	57.062
	1962–1963 (N = 38)	0.068	100.00%	100.00%	62.094	48.128	145.555	52.073	9.666	27.703	92.701	138.596
	1964–1966 (N = 31)	0.068	100.00%	100.00%	56.274	44.189	144.373	49.873	8.833	35.533	88.991	131.732
PFHxS	1960–1961 (N = 28)	0.041	96.43%	96.43%	7.370	5.120	18.440	7.715	0.735	2.283	11.361	15.291
	1962–1963 (N = 38)	0.041	100.00%	100.00%	22.591	16.04	92.540	20.336	2.398	10.400	28.598	67.348
	1964–1966 (N = 31)	0.041	100.00%	100.00%	22.836	19.177	65.166	18.330	7.000	13.970	33.218	55.333
PFOA	1960–1961 (N = 28)	0.041	96.43%	96.43%	5.201	4.45	14.488	4.756	1.871	2.736	6.201	9.824
	1962–1963 (N = 38)	0.041	100.00%	100.00%	7.355	6.414	14.148	6.427	2.610	3.873	10.363	13.668
	1964–1966 (N = 31)	0.041	100.00%	100.00%	9.033	8.262	19.158	7.831	4.640	5.791	10.984	18.056
PFHpS	1960–1961 (N = 28)	0.039	100.00%	100.00%	0.837	0.479	6.890	0.568	0.056	0.334	0.867	1.528
	1962–1963 (N = 38)	0.039	97.37%	97.37%	1.328	0.967	4.981	1.153	0.121	0.591	1.890	2.923
	1964–1966 (N = 31)	0.039	100.00%	100.00%	1.330	0.935	4.090	1.223	0.125	0.685	1.500	3.450
PFNA	1960–1961 (N = 28)	0.033	96.43%	100.00%	0.390	0.255	2.342	0.323	0.042	0.155	0.445	0.875
	1962–1963 (N = 38)	0.033	97.37%	100.00%	0.378	0.277	1.584	0.305	0.056	0.181	0.445	1.029
	1964–1966 (N = 31)	0.033	96.77%	100.00%	0.607	0.349	2.565	0.426	0.035	0.275	0.825	1.888
8:2-FTS	1960–1961 (N = 28)	0.038	64.29%	64.29%	1.279	1.048	2.343	1.320	0.103	0.878	1.636	2.343
	1962–1963 (N = 38)	0.038	89.47%	92.11%	2.154	1.469	5.535	2.261	0.243	0.970	2.835	5.301
	1964–1966 (N = 31)	0.038	100.00%	100.00%	2.652	2.088	7.625	2.500	0.581	1.188	3.131	6.945

Table 4
Associations[a] between log-transformed maternal serum PFAS levels (ng/mL) during pregnancy and birth outcomes.

	Birth Weight		Birth Length		Infant Ponderal Index at birth	
	Crude β(P value)	Adjusted[b] β(P value)	Crude β(P value)	Adjusted[b] β(P value)	Crude β(P value)	Adjusted[b] β(P value)
PFOS ≥Median	−0.307(0.003)	−0.323(0.006)	−0.955(0.060)	−1.165(0.059)	−0.110(0.043)	−0.088(0.228)
PFHxS ≥Median	−0.275(0.008)	−0.292(0.015)	−0.502(0.327)	−0.468(0.455)	−0.154(0.004)	−0.168(0.02)
PFOA ≥Median	−0.317(0.002)	−0.233(0.030)	−1.203(0.017)	−1.021(0.065)	−0.081(0.136)	−0.037(0.571)
PFHpS ≥Median	−0.219(0.036)	−0.239(0.023)	−0.625(0.221)	−0.724(0.186)	−0.094(0.084)	−0.093(0.148)
PFNA ≥Median	−0.236(0.024)	−0.239(0.017)	−0.543(0.289)	−0.490(0.349)	−0.108(0.047)	−0.115(0.058)
NMeFOSAA ≥Median	0.005(0.963)	−0.045(0.674)	−0.213(0.678)	−0.556(0.308)	0.045(0.414)	0.064(0.318)
PFPeS ≥Median	−0.152(0.149)	−0.143(0.161)	−0.295(0.564)	−0.145(0.783)	−0.078(0.154)	−0.092(0.136)
NEtFOSAA ≥Median	−0.051(0.628)	−0.036(0.744)	−0.46(0.369)	−0.744(0.187)	0.023(0.669)	0.074(0.266)
8:2-FTS ≥Median	−0.085(0.42)	−0.062(0.587)	−0.172(0.738)	−0.270(0.644)	−0.046(0.400)	−0.008(0.906)
PFPeA ≥Median	−0.030(0.776)	−0.075(0.468)	−0.460(0.369)	−0.587(0.27)	0.036(0.515)	0.022(0.725)
PFHxA ≥Median	−0.225(0.031)	−0.180(0.084)	−0.419(0.413)	0.074(0.892)	−0.121(0.025)	−0.148(0.018)

[a] With serum levels < Median as the reference group for all comparisons.
[b] Adjusted for maternal age at pregnancy (years); weight change in pounds during pregnancy (lbs); duration of gestation in days; marital status (married vs other), parity (0 or 1); number of cigarettes smoked per day during pregnancy (none, <1 pack/day, and ≥1 pack/day); family socioeconomic index (in tertiles); race (white vs other); year of blood collection (1960–1961 vs 1962–1963 vs 1964–1966); and child sex.

Table 5
Associations between log-transformed maternal serum PFAS levels (per unit) during pregnancy and birth outcomes.

	Birth Weight		Birth Length		Infant Ponderal Index	
	Crude β(P value)	Adjusted[a] β(P value)	Crude β(P value)	Adjusted[a] β(P value)	Crude β(P value)	Adjusted[a] β(P value)
PFOS	−0.219(0.034)	−0.159(0.177)	−0.216(0.670)	0.124(0.839)	−0.143(0.007)	−0.142(0.045)
PFHxS	−0.182(0.068)	−0.153(0.179)	−0.006(0.990)	0.213(0.718)	−0.147(0.004)	−0.153(0.024)
PFOA	−0.355(0.017)	−0.228(0.156)	−0.739(0.310)	−0.294(0.725)	−0.174(0.023)	−0.134(0.166)
PFHpS	−0.135(0.227)	−0.117(0.291)	−0.152(0.781)	−0.079(0.890)	−0.095(0.101)	−0.092(0.167)
PFNA	−0.200(0.086)	−0.173(0.143)	−0.469(0.410)	−0.293(0.633)	−0.084(0.163)	−0.083(0.245)
NMeFOSAA	0.140(0.168)	0.085(0.409)	0.305(0.538)	0.065(0.903)	0.074(0.160)	0.071(0.255)
PFPeS	−0.053(0.599)	−0.105(0.286)	0.013(0.980)	−0.169(0.741)	−0.040(0.444)	−0.055(0.356)
NEtFOSAA	−0.063(0.491)	−0.099(0.287)	−0.317(0.473)	−0.713(0.134)	−0.005(0.917)	0.023(0.684)
8:2-FTS	−0.011(0.878)	0.001(0.995)	−0.073(0.828)	−0.112(0.778)	0.00002(0.999)	0.017(0.712)
PFPeA	0.018(0.810)	0.015(0.841)	0.157(0.674)	0.243(0.523)	−0.014(0.717)	−0.027(0.543)
PFHxA	−0.113(0.251)	−0.077(0.431)	0.050(0.916)	0.516(0.307)	−0.102(0.042)	−0.135(0.020)

[a] Adjusted for maternal age at pregnancy (years); weight change in pounds during pregnancy (lbs); duration of gestation in days; marital status (married vs other), parity (0 or 1); number of cigarettes smoked per day during pregnancy (none, <1 pack/day, and ≥1 pack/day); family socioeconomic index (in tertiles); race (white vs other); year of blood collection (1960–1961 vs 1962–1963 vs 1964–1966); and child sex.

PFOA, PFHpS and PFNA had significantly lower birth weight. A significant negative association was also observed between infant Ponderal Index with maternal serum levels of PFOS, PFHxS, PFHpS, PFNA and PFHxA. Among women who gave birth to girls, higher serum levels of PFHxS, PFHpS, and 8:2-FTS were associated with a significant negative association with infant Ponderal Index at birth.

Compared to the measures (Table 6) reported in reproductive-age women in the National Health and Nutrition Examination Survey (NHANES)(CDC (Centers for Disease Control and Prevention), 2019), the blood serum level geometric mean of 36.02 ng/mL for PFOS that we observed from samples collected in 1960-66 was much higher than the blood plasma level geometric mean of 10.70 ng/mL in 2007–2008 of the NHANES reproductive age women. However, our mean PFOS level was comparable to that reported serum median level of PFOS (32.10 ng/mL) from the blood samples collected in 1959-67 among the control women from the California Child Health and Development Studies pregnancy cohort – a group comparable to the current sample (Cohn et al., 2020). The blood serum level geometric mean of 12.01 ng/mL for PFHxS found in the current samples was also much higher than the reported geometric mean of 1.46 ng/mL in these reproductive-age women in 2007–2008 in these NHANES reproductive age women. The geometric mean of 6.28 ng/mL for PFOA from this study was also higher than that of 3.55 ng/mL of the reproductive-age women in 2007–2008. Our study also has much higher serum levels of these major PFAS than that of reported from another recent study of pregnant women in the United States (DeLuca et al., 2023). In fact, our study has the highest serum levels of PFOS and PFHxS reported in pregnant women as compared in Table 6. Our mean PFOA level was also only lower than those reported from pregnant women in Mid-Ohio Valley community knowing exposed to high levels of PFOA through drinking-water contamination(Stein et al., 2009; Darrow et al., 2013), and from Guiyu (Wu et al., 2012), China, a primitive electronic waste recycling area; and from Shanghai (Huo et al., 2020) with blood samples collected 2013-16.

While our study is a small pilot, we found a significant negative

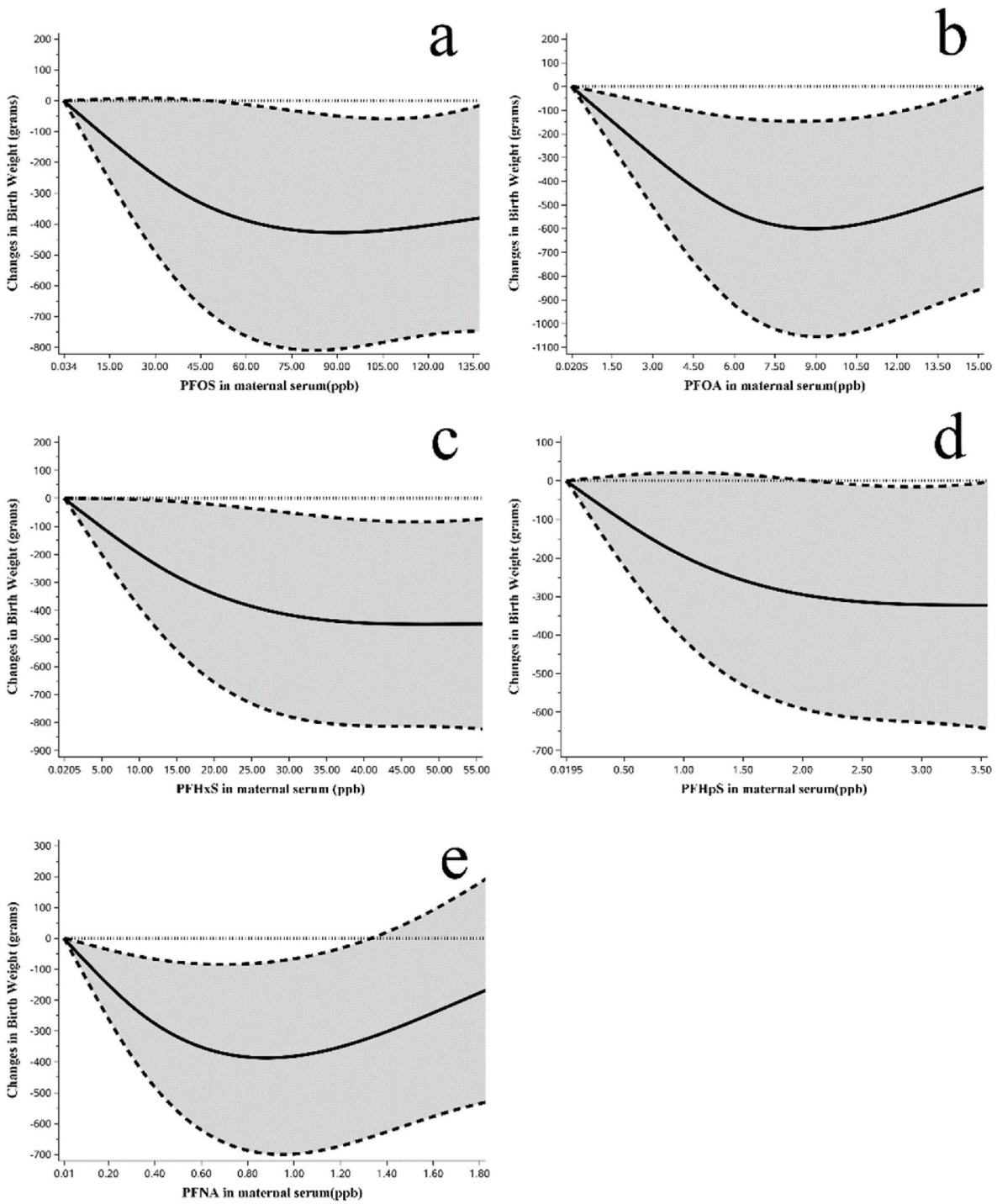

Fig. 1. Adjusted restricted cubic spline analyses of the association between PFOS (a), PFOA (b) PFHxS (c), PFHps (d) and PFNA (e) in maternal serum (ng/mL) during pregnancy and birth weight. The lines show the estimates (−) and the 95% confidence intervals (—). Models adjusted for maternal age at pregnancy (years); weight change in pounds during pregnancy (lbs); duration of gestation in days; marital status (married vs other), parity (0 or 1); number of cigarettes smoked per day during pregnancy (none, <1 pack/day, and ≥1 pack/day); family socioeconomic index (in tertiles); race (white vs other); year of blood collection (1960–1961 vs 1962–1963 vs 1964–1966); and child sex.

association between maternal serum levels of PFOS, PFHxS, PFOA, PFHpS and PFNA during pregnancy and birth weight. Prior studies that have used biosamples collected after 1990s have reported an association between maternal serum or cord blood PFOA/PFOS concentrations and adverse birth outcomes while the results have not been consistent. (Bach et al., 2016; Chen et al., 2012; Fei et al., 2007; Monroy et al., 2008; Robledo et al., 2014; Savitz et al., 2012a,b). Although the precise mechanisms underlying these associations have not been established, several potential pathways have been proposed linking prenatal PFAS exposure to impaired fetal development and birth size in humans including hormone disruption, inducing *reactive oxygen species* (*ROS*) production; altered lipid metabolism, and immunotoxicity in pregnant women and their developing fetus.

Thyroid hormones are pivotal for normal fetal growth and development. PFOA/PFOS exposures are able to alter thyroid hormone signaling and interfere with thyroid hormone function and homeostasis,

Table 6
Comparisons of the serum levels (ng/mL) of PFAS in our study population to that of the NHANES and pregnant women in the world from published epidemiologic studies.

Authors	Population	Years Blood Collected	PFOS	PFOA	PFHxS	PFNA	Remarks
USA							
Zheng et al.	Current study	1960–66	36.26	6.30	12.01	0.29	Geometric mean
NHANES (CDC (Centers for Disease Control and Prevention), 2019)	US	2007–08	10.70	3.55	1.46	1.09	Geometric mean
Cohn et al. (Cohn et al., 2020)	California	1959–67	32.10	0.40	2.30		Median (controls)
Sagiv et al. (Sagiv et al., 2018)	Massachusetts	1999–02	25.70	5.80	2.40	0.70	Median (plasma)
Shoaff J et al. (Shoaff et al., 2018)	Ohio	2003–06	14.00	5.50	1.20	0.82	Median
Kato et al. (Kato et al., 2014)	Ohio	2003–06	12.70	4.80			Median
Stein et al. (Stein et al., 2009)	Ohio	2005–06	13.60	21.20			Median
Louis et al. (Louis et al., 2016)	Michigan-Texas	2005–09	12.20	3.30		1.20	Median
Darrow et al. (Darrow et al., 2013)	Ohio	2005–06	15.60	31.00			Mean
Starling et al. (Starling et al., 2017)	Colorado	2009–14	2.30	1.04	0.75	0.39	Mean
Eick et al. (Eick et al., 2020)	San Francisco	2014–18	1.93	0.76	0.33	0.30	Median
Rest of the world							
Marks et al. (Marks et al., 2019)							
Maisonet et al. (Maisonet et al., 2012)	UK	1991–92	19.60	3.70	1.60		Median
Whitworth et al. (Whitworth et al., 2012)	Norway	1999–08	13.00	2.20			Median
Washino et al. (Washino et al., 2009)	Japan	2002–05	5.60	1.40			Mean
Kwon et al. (Kwon et al., 2016)	Korea	2006–10	0.54	0.89	0.36	0.18	Median
Hamm et al. (Hamma et al., 2010)	Canada	2006–07	9.00	2.10	2.10		Mean
Wu et al. (Wu et al., 2012)	China	2007		18.32			Mean
Martin et al. (Ashley-Martin et al., 2017)	Canada	2008–11	4.60	1.70	1.00		Median
Callan et al. (Callan et al., 2016)	Australia	2008–11	2.32	1.00	0.47	0.30	Mean
Bach et al. (Bach et al., 2016)	Denmark	2008–13	8.30	2.00	0.50	0.80	Median
Liu et al. (Liu et al., 2020)	China	2009–13	1.79	0.79			Median
Souza et al. (Souza et al., 2020)	Brazil	2010–11	5.93	0.27			Mean
Jensen1 et al. (Jensen et al., 2015)	Denmark	2010–12	7.06	1.51		0.65	Median
Lee et al. (Lee et al., 2013)	Korea	2011	10.77	2.73	1.35		Mean
Huo et al. (Huo et al., 2020)	China	2013–16	9.33	11.85	0.54	1.69	Median
Wang et al. (Wang et al., 2019)	China	2013	1.10	2.64			Mean

and this could trigger developmental and maternal hypothyroidism, which is associated with low birth weight (Washino et al., 2009; White et al., 2011; Andersen et al., 2008). Estrogen has been demonstrated to be important in promoting fetal growth. Some PFAS, including PFOA, are recognized as endocrine-disrupting chemicals (EDCs) that can influence estrogen homeostasis (Jensen and Leffers, 2008; Sakai et al., 2022; Kjeldsen and Bonefeld-Jørgensen, 2013). Growing body of evidence indicates that PFAS exposure promotes oxidative stress, which may be particularly detrimental to maternal and fetal health (Taibl et al., 2022). Oxidative stress *in utero* impacts the normal course of pregnancy (Go and Jones, 2017; Marseglia et al., 2014). A study of a cohort of newborns from China showed significantly higher levels of serum ROS levels in the fourth quartile group in cord blood plasma compared with the lowest quartile (Liu et al., 2018).

PFAS are involved in cholesterol metabolism and epidemiologic studies have shown a significant association between PFAS exposures and total cholesterol and low-density lipoprotein (LDL) cholesterol in different populations (Haug et al., 2023). The fetus is sensitive to the availability of cholesterol and triglycerides, which support cellular growth, differentiation and adipose accumulation (Apelberg et al., 2007). Evidence from both experimental and epidemiological studies, strongly support that PFAS affect multiple aspects of the immune system (Ehrlich et al., 2023). PFAS exposure to impaired fetal growth and reduced birth weight may also include immunotoxicity resulting in increased susceptibility to infection in pregnant women, considering the developing immune system of fetus is especially vulnerable to PFAS toxic insults (Ehrlich et al., 2023).

Our study for the first time (to our knowledge) examined the potential impact of PFAS on birth outcomes using the blood samples collected in the early 1960s, a time period following the start of the widespread use of PFAS in industry and in consumer products. Our study participants had much higher PFAS levels than those reported by most recent studies, where the blood samples were collected after the voluntary phase-out of PFOS and PFOA in the early2000s due to the alleged association between PFAS exposure and adverse health outcomes (EPA, 2019).

A limitation of our study is its small sample size, and thus, while we observed an overall negative association between various PFAS exposure and birth outcomes, few of our observations reached statistically significant levels. Further, we did not correct for multiple comparisons so we cannot rule out the role of chance as the potential explanation for the significant associations observed in this study. We did not look at the effects of PFAS mixtures in the study.

In conclusion, this study provides additional data suggesting that elevated serum levels of PFAS in pregnant women may be associated with lower infant birth weight, particularly for PFOS, PFHxS, PFOA, PFHpS and PFNA. We also demonstrated pregnant people in this cohort enrolled in the 1960s have high levels of PFAS and, thus, cohort studies with banked serum specimens from early time periods could be unique resources for the evaluation of the association between prenatal PFAS exposure and adverse health outcomes.

Credit author statement

Stephen Buka, Tongzhang Zheng, Karl Kelsey: Conceptualization, methodology, writing original draft and editing. Cairong Zhu, Qiang Yao, George Papandonatos and Yafei Zheng: Data analyses, methodology, review and editing. Kurt Pennell and Katherine Manz: Laboratory chemical analyses, methodology, review and editing. Joseph Braun, Yun Liu, Qingming Liu, Kunchong Shi, and Siri Brochman: Methodology, review and editing and supervision.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Braun was compensated for serving as an expert witness on behalf of plaintiffs in litigation related to PFAS-contaminated drinking water.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.117010.

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