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Prenatal exposure to per- and polyfluoroalkyl substances, fetoplacental hemodynamics, and fetal growth

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ABSTRACT

Introduction: The impact of legacy per- and polyfluoroalkyl substances (PFAS) on fetal growth has been well studied, but assessments of next-generation PFAS and PFAS mixtures are sparse and the potential role of fetoplacental hemodynamics has not been studied. We aimed to evaluate associations between prenatal PFAS exposure and fetal growth and fetoplacental hemodynamics.

Methods: We included 747 pregnant women from the BiSC birth cohort (Barcelona, Spain (2018–2021)). Twenty-three PFAS were measured at 32 weeks of pregnancy in maternal plasma, of which 13 were present above detectable levels. Fetal growth was measured by ultrasound, as estimated fetal weight at 32 and 37 weeks of gestation, and weight at birth. Doppler ultrasound measurements for uterine (UtA), umbilical (UmA), and middle

Abbreviations: BWQS, Bayesian Weighted Quartile Sums; BMI, body mass index; GAMM, generalised additive mixed model; PFAS, Per- and Polyfluorinated Substances; PFBA, Perfluorobutanoate; PFPeA, Perfluoropentanoate; PFHxA, Perfluorohexanoate; PFHpA, Perfluoroheptanoate; PFOA, Perfluorooctanoate; PFNA, Perfluorononanoate; PFDA, Perfluorodecanoate; PFUnDA, Perfluoroundecanoate; PFDoDa, Perfluorododecanoate; PFTrDa, Perfluorotridecanoate; PFTeDa, Perfluorotetradecanoate; PFBS, Perfluorobutane sulfonate; PFHxS, Perfluorohexane sulfonate; PFHpS, Perfluoroheptane sulfonate; PFOS, Perfluorooctane sulfonate; PFDS, Perfluorodecane sulfonate; PFOSA, Perfluorooctane sulfonamide; MeFOSA, N-Methylperfluorooctane sulfonamide; EtFOSA, N-Ethylperfluorooctane sulfonamide; HFPO-DA or GenX, Ammonium salt of 2,3,3,3,-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-propanoate; ADONA, Ammonium salt of 4,8-dioxa-3H-perfluorononanoate; 6:2 Cl-PFESA, 6:2 chlorinated polyfluoroalkyl ether sulfonate; 8:2 Cl-PFESA, 11-chlorohexadecafluoro-3-oxanonane-1- sulfonate; LC-MS/MS, Liquid chromatography coupled to tandem mass spectrometry.

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cerebral artery (MCA) pulsatility indices (PI), as well as the cerebroplacental ratio (CPR – ratio MCA to UmA), were obtained at 32 weeks to assess fetoplacental hemodynamics. We applied linear mixed effects models to assess the association between singular PFAS and longitudinal fetal growth and PI, and Bayesian Weighted Quantile Sum models to evaluate associations between the PFAS mixture and the aforementioned outcomes, controlled for the relevant covariates.

Results: Single PFAS and the mixture tended to be associated with reduced fetal growth and CPR PI, but few associations reached statistical significance. Legacy PFAS *PFOS*, *PFHpA,* and *PFDoDa* were associated with statistically significant decreases in fetal weight z-score of 0.13 (95%CI (−0.22, −0.04), 0.06 (−0.10, 0.01), and 0.05 (−0.10, 0.00), respectively, per doubling of concentration. The PFAS mixture was associated with a non-statistically significant 0.09 decrease in birth weight z-score (95%CI −0.22, 0.04) per quartile increase.

Conclusion: This study suggests that legacy PFAS may be associated with reduced fetal growth, but associations for next generation PFAS and for the PFAS mixture were less conclusive. Associations between PFAS and fetoplacental hemodynamics warrant further investigation.

1. Introduction

Exposure to highly persistent per- and polyfluoroalkyl substances (PFAS), used extensively in industrial and commercial products, continues in the human population, despite growing concerns about toxicity to human health (Fenton et al., 2021; Panieri et al., 2022; Cousins et al., 2022). PFAS are recognized endocrine disruptors, degrade minimally in the environment, and accumulate in the body over time, potentially contributing to associated health outcomes (Fenton et al., 2021; Coperchini et al., 2021; Di Nisio et al., 2022). Environmental agencies recognize over 15,000 PFAS; however, only a small fraction has been extensively studied (CompTox Chemicals Dashboard, 2023; Williams et al., 2022). As health data accumulates regarding 'legacy' PFAS such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), certain PFAS have been phased out and replacement compounds are now widely used. 'Next generation' PFAS, those meant to replace legacy PFAS (e.g., GenX, 6.2.Cl-PFESA), typically have shorter carbon chains and in some cases have not yet been detected in human populations (Mahoney et al., 2022; Heydebreck et al., 2015; Göckener et al., 2020). Importantly, the effects and safety of 'next generation' PFAS remain unclear (Espartero, 2022; Pelch et al., 2022; Nian et al., 2022; Calafat et al., 2019; Manojkumar et al., 2023; Li et al., 2021).

Widespread human exposure to PFAS occurs via drinking water, food, or respiratory pathways leading to bioaccumulation and increased risk of negative health outcomes, even at low levels of exposure (Cousins et al., 2022; Sunderland et al., 2019). Evidence shows that PFAS cross the placental barrier and have been found in the placental tissue, cord blood, fetal organs, and breast milk, raising concerns about the potential effects on the developing fetus (Cai et al., 2020; Xu et al., 2023; Müller et al., 2019; Lu et al., 2021; Mamsen et al., 2017). Systematic reviews of studies examining fetal growth and PFAS have generated cause for concern surrounding the potential toxic effects of PFAS in developing fetuses (Bach et al., 2015; Gui et al., 2022). While many epidemiological studies have shown the likely association between prenatal PFAS exposure and reduced birth weight, less investigate the effects on fetal biometry across pregnancy (Costa et al., 2019; Manzano-Salgado et al., 2017; Kashino et al., 2020; Sevelsted et al., 2022; Ouidir et al., 2020) or the role of the placenta (Szilagyi et al., 2020; Gan et al., 2024; Hall et al., 2022).

Fetal growth hinges upon proper placental function and homeostasis of fetoplacental hemodynamics. This includes adequate perfusion and nutrient transfer between maternal, placental, and fetal units (Morley et al., 2021). As a part of routine clinical antepartum surveillance, fetoplacental hemodynamics are assessed via Doppler pulsatility indices (PI) of the uterine (UtA), umbilical (UmA), and middle cerebral (MCA) arteries. Previous research has demonstrated the association between abnormal UtA and UmA PI and intrauterine growth restriction, while changes to the MCA and the cerebroplacental ratio (MCA/UmA) can indicate fetal adaptations to redistributions of blood flow and signal possible fetal compromise or other adverse perinatal outcomes (Figueras et al., 2006; Simonazzi et al., 2013; Oros et al., 2019). Environmental exposures may disrupt the maternal endocrine system and fetal growth via perturbations of fetoplacental hemodynamics (Coperchini et al., 2021). Early alterations of fetoplacental hemodynamics may lead to altered nutrient transfer capacity as pregnancy advances (Myatt et al., 2012). Alternatively, disruptions in hormone activity within the maternal-fetal unit may affect fetal metabolic programming and fat storage, or the transfer of PFAS may have a toxic effect to the fetal endocrine system directly (Szilagyi et al., 2020; Wieser et al., 2008).

Previous cohort studies have assessed longitudinal associations between PFAS and fetal growth and birth weight (Bach et al., 2015; Gui et al., 2022; Costa et al., 2019; Manzano-Salgado et al., 2017; Kashino et al., 2020; Wikström et al., 2020; Callan et al., 2016; Kaiser et al., 2023; Chen et al., 2021; Padula et al., 2023; Mahfouz et al., 2023; Steenland et al., 2018); however, studies on a broader range of 'legacy' and 'next-generation' PFAS are scarce and inconsistent. Few studies have examined joint effects of multiple PFAS present in human blood and even fewer have examined the influence on in-utero fetal biometry during pregnancy (Costa et al., 2019; Manzano-Salgado et al., 2017; Papadopoulou et al., 2021; Kalloo et al., 2020; van den Dries et al., 2021), while no study has examined fetoplacental hemodynamics via pulsatility indices in association with maternal PFAS concentrations. Investigating PFAS exposure during pregnancy provides insights into how changes in fetoplacental hemodynamics, as indicators of placental function, can affect fetal growth and development. This study aimed to evaluate the relationship between in-utero exposure to multiple legacy and next-generation PFAS, and fetoplacental hemodynamics and fetal growth.

2. Methods

2.1. Study population

We used data from the Barcelona Life Study Cohort (BiSC), comprising 1080 pregnant women recruited during the first routine prenatal visit (11–15 weeks) at three tertiary university hospitals in Barcelona, Spain. A detailed description of the recruitment process, follow-ups, and data collection are presented elsewhere (Dadvand et al., 2024). Briefly, mothers were included if they (i) had singleton pregnancy, (ii) were aged 18–45 years, (iii) could communicate in Spanish/Catalan, (iv) were residents of the study area, and (v) planned to give birth in one of the recruiting hospitals. The current study included 747 mothers with data on prenatal PFAS exposure at 32 weeks of gestation, at least two fetal growth measurements (32– or 37- weeks of gestation or birth), and documented gestational age. A subset of 723 had PI at 32 weeks (Figure S1). All participating women provided informed consent. Ethics approvals were obtained from the corresponding authorities in all the participating institutions and hospitals (Table S1).

2.2. PFAS exposure

Maternal blood samples were collected at 32 weeks of gestation

(mean = 32.1; SD = 1.2) and analyzed for 23 PFAS (Table S2) in plasma using high-performance liquid chromatography and tandem mass spectrometry (LC-MS/MS) according to a previously validated and published method (Haug et al., 2009). The limit of quantification (LOQ) was 0.050 ng/mL for all PFAS except for PFBA (1.0 ng/mL), 6:2Cl-PFESA (LOQ = 0.01 ng/mL), PFTeDa, PFDS, and HFPO-DA (GenX) (LOQ = 0.20 ng/mL). Blanks showed no PFAS above the LOQ. Thirteen of the 23 PFAS analyzed were detected and included in the statistical analysis: PFUnDA, PFTrDA, PFOSA, PFOS, PFOA, PFNA, PFHxS, PFHpS, PFHpA, PFDoDa, PFDA, PFBS, 6:2Cl-PFESA. PFTeDA and PFBA were excluded because 99.9 % of values were below LOD.

2.3. Fetal growth standard scores and pulsatility indices

2.3.1. Fetal growth standardized scores

Fetal growth measurements for the 32-week (mean = 31.7; SD = 1.2) BiSC visits were performed by trained obstetrician investigators, while 37-week (mean = 36.1; SD = 1.2) fetal growth data were obtained during routinely scheduled antenatal care visits by specialized obstetricians following the hospital standardized protocols. Estimated fetal weights (EFW) were calculated from ultrasound measurements of fetal head circumference (HC), femur length (FL), and abdominal circumference (AC) using Hadlock's formula III at 32– and 37-weeks gestation (Hadlock et al., 1985). Biparietal diameter (BPD) was also collected and measured at the transverse plane from the outer border to the inner border of the skull. Data on birth weight was obtained from the hospital medical record of the neonate. Gestational age was calculated by clinicians using the crown-rump-length (CRL) from the approximately 12th week obstetrical visit (Altman and Chitty, 1997). Because fetal size can be confounded by gestational age, standard scores are preferred over raw estimated fetal weight and birth weight (Callaghan and Dietz, 2010). For all measurements (HC, BPD, FL, AC) the interquantile range was determined using linear interpolation and the World Health Organization (WHO) fetal growth curves as a reference (Kiserud et al., 2017). Then, sex-specific and adjusted for gestational age standard scores were derived for each fetus and used as the outcome at each time point (Kiserud et al., 2017).

2.3.2. Pulsatility indices

Fetoplacental hemodynamics, assessed by pulsatility indices (PI) obtained via Doppler velocimetry measurements, are commonly employed by gynecologists to evaluate maternal and fetal well-being, offering insights into potential mechanisms that contribute to abnormal fetal growth (Pettker and Campbell KH, 2024). Specifically, PI of the uterine (UtA), umbilical (UmA), and middle cerebral arteries (MCA) reflect changes in perfusion to the fetoplacental unit and may be indicators of placental insufficiency, fetal compensatory adaptation, or intrauterine growth restriction (IUGR) (Myatt et al., 2012; Pettker et al., 2024; NICE, 2019; Shahinaj et al., 2010; Tian and Yang, 2022; Fox et al., 2019). In the current study, PI of the UtA and UmA were obtained via doppler ultrasound examination at 32 and 37 weeks by a trained obstetrician and assessed by a hospital clinician prior to being documented in the participant's medical record. UtA PI were obtained transabdominally using color doppler on the ultrasound machine. Bilateral measurements were taken at the point of the external iliac artery intersection. These informed the mean for the right and left reading, which were then averaged to obtain the mean UtA PI. The UmA PI was measured from a free-floating cord loop. The MCA PI was obtained using a transversal view of the fetal head, at the level of its origin from the circle of Willis (Figueras et al., 2006). The cerebroplacental ratio (CPR) was calculated as a ratio of the MCA PI to UmA PI (Baschat and Gembruch, 2003). Doppler parameters were performed from three or more consecutive waveforms, with the angle of insonation as close to zero as possible, and the PI measurements were automatically calculated by the ultrasound machine (Baschat and Gembruch, 2003; Figueras et al., 2006). Standard scores were created for each pulsatility index (UtA, UmA, MCA, CPR) using published reference range values obtained from a population of pregnancies without complications (Baschat and Gembruch, 2003; Gómez et al., 2008; Arduini and Rizzo, 1990). In our final statistical analyses, we only used the pulsatility indices measured at 32 weeks, and not those measured at 37 weeks, because the latter were restricted to a small subset of women (N = 173) where the clinician suspected pregnancy complications.

2.4. Maternal and newborn covariates

Maternal socio-demographic (age, ethnicity, and education) and pregnancy related variables (BMI, parity, previous breastfeeding, pathologies etc.) were collected through questionnaires administered by study investigators and medical record review during the third trimester at the 32 weeks antenatal visit and at birth. During the second trimester (20 weeks of pregnancy), mothers completed an online 100-item food frequency questionnaire (FFQ) that was used to assess the usual dietary intake during pregnancy (Vioque et al., 2013). The response to each food item was calculated to an average daily intake in grams for each participant. Regarding seafood consumption (g/day), a range of types were assessed: salmon, shellfish, tuna, hake, blue fish, and if the mother took omega-3 supplements during pregnancy. Newborn sex and type of delivery (i.e., vaginal, instrumental or cesarean) were collected from clinical records.

2.5. Statistical analysis

PFAS concentrations below LOD with observable signals from the LC-MS/MS device were included in the statistical analysis. For samples in which no values were generated (no signal from the LC-MS/MS device), singly imputed data were obtained using a quantile regression approach for the imputation of left-censored missing data implemented in the *imputeLOD* function in the "rexposome" package in the R software (v4.2.3; R Core Team 2023) (Gardner et al., 2021; imputeLCMD-package function, 2023). PFAS were $\log_2$ transformed to correct right-skewed distributions. Pairwise Pearsońs correlation coefficients examined correlations between PFAS. Hierarchical clustering patterns were determined by correlation distance ($1 - r$) to assess the similarities and dissimilarities of PFAS across observations. We performed generalized additive mixed models (GAMMs) using the "mgcv" package in R to assess linearity in the relationship between the $\log_2$ transformed PFAS and fetal and placental outcomes. In addition to visual interpretations, if the effective degrees of freedom were equal or close to 1, the relationship was considered close to linear. Most GAMMs showed evidence of linearity with few exceptions (Fig S3-S4). When there was deviation from linearity, we additionally modeled PFAS concentrations as categorical variables (tertiles) in the subsequent regression models.

Analyses consisted of the complementary use of linear regression, linear mixed effect and Bayesian weighted quantile sum (BWQS) models. Linear mixed models were used to assess the association between each singular PFAS and overall fetal growth during the third trimester until birth. Linear mixed models included each single PFAS exposure and each repeated fetal growth measurements AC, BPD, FL, HC/HC at birth, and EFW/birth weight. All models utilized participant ID as the random intercept to account for the correlations between repeated measurements within each subject. In linear mixed models, we imputed missing values in covariate data using multiple imputations by chained equations generating 20 datasets using the "mice" package in R (Table S3). Results from use of the imputed data sets were combined using Rubińs combination rules (van Buuren, 2018). Linear regression models were used to evaluate associations between single PFAS exposures and pulsatility measurements assessed at 32 weeks. BWQS models were used to assess the potential joint effects of the PFAS mixture on fetal growth and fetoplacental hemodynamics. BWQS models included the PFAS mixture in association with each fetal growth parameter (AC, BPD, FL, HC and EFW) at 32 and 37 weeks, and HC and weight at birth,

and for the pulsatility indices (UmA, UtA, CPR) at 32 weeks. The BWQS model is an extension of the WQS model and allows for a broader, untargeted approach when exploring relationships among unspecified variables (Colicino et al., 2019). BWQS summarizes the exposure of the entire mixture of measured PFAS by estimating a single weighted index and accounting for the individual contribution of each singular component using weights. Contrary to WQS, BWQS allows more flexibility since it does not require directionality of the coefficient associated with the mixture (Colicino et al., 2019; Colicino et al., 2023). For our BWQS models, we used the first imputed data set.

Covariates were selected using a directed acyclic graph (DAG) (Dagitty software) based on a priori knowledge (Fábelová et al., 2023; Silvestrin et al., 2013; Park et al., 2019; Clayborne et al., 1982; Hinkle et al., 2014; Shah, 2010; Palatnik et al., 2020) (Fig. 2a-b). The regression model for fetal growth included maternal BMI at 12 weeks gestation (kg/m^2), maternal education completed (primary, secondary, university), ethnicity (European, Latin American, Other), hospital, maternal age at 12 weeks of gestation (years), parity (number of previous pregnancies $\geq$ 20 completed weeks), seafood diet (grams/day), and smoking during pregnancy (no/yes). The regression model for pulsatility indices included maternal BMI at 12 weeks gestation (kg/m^2), maternal age at 12 weeks of gestation, parity, hospital, seafood diet (grams/day) and smoking during pregnancy (none/yes).

Further, we conducted the following stratified analyses. To explore the presence of effect modifiers in fetal development, we stratified the linear mixed models and BWQS models (at each time point) by fetal sex. We also tested for interaction using the cross-product term fetal sex in all models. To explore changes in effect by time windows of fetal development, we stratified single PFAS exposure models by prenatal visit (32– and 37- weeks) and birth, and tested for interaction by inserting the cross-product terms for time window. To explore the potential influence of hypertensive disorders during pregnancy on fetal growth, we further restricted the study population to those without a diagnosis of de novo or chronic hypertension, including preeclampsia and assessed the results of linear mixed models.

We defined statistical significance as results having a p-value of $<$ 0.05. For interaction terms, we considered a more relaxed p-value of 0.10. Data cleaning, GAMMs and linear mixed models were performed using RStudio version 4.3.2. BWQS models were performed using RStudio version 4.3.0. (RStudio Team, 2023).

3. Results

3.1. Study population characteristics

Characteristics of the BiSC participants included and excluded in the study are detailed in Table 1. Included women were on average 34 years-old, and the majority were of European ethnicity, with university education, and nulliparous. There was little difference between the characteristics of the study sample and the excluded mothers, except for hospital of birth (driven by hospital B, Table 1). Newborns included in this study population weighed on average 3306 g at birth and had completed 278 days (39.7 weeks) of gestation (Table 1). Included newborns were born at a slightly later gestational age, weighed more, and had larger head circumferences than those excluded from our study (Table 1).

3.2. PFAS exposure

Thirteen PFAS were detected and included in the statistical analysis: PFUnDA, PFTrDA, PFOSA, PFOS, PFOA, PFNA, PFHxS, PFHpS, PFHpA, PFDoDa, PFDA, PFBS, 6:2Cl-PFESA (Fig. 1). PFTeDA and PFBA were excluded because 99.9 % of values were below LOD (Table S4). For the thirteen PFAS, concentrations were above the LOD for the majority of samples (50.3 – 100.0 %) (Table S4). In general, concentrations of legacy PFASs, namely PFOS, PFOA, PFHxS and PFNA, were found in the

Table 1
Study population characteristics in comparison to the subsample of excluded BiSC participants, percent missing of covariates from the included population and after imputation averages.

	Study population N = 747			Excluded participants N = 333
	Mean ± SD or n (%)	Missing values N (%)	Imputed data Mean ± SD or n (%)	Mean ± SD or n (%)
Maternal Characteristics				
Age (years)	34.1 ± 4.7	0 ± 0.0	34.1 ± 4.7	34.1 ± 4.9
Ethnicity		0 (0.0)		
European	550 (73.6)		550 (73.6)	246 (73.9)
Latin American	181 (24.2)		181 (24.2)	79 (23.7)
Other	16 (2.1)		16 (2.14	8 (2.4)
Education completed		0 (0.0)		
Primary or less	33 (4.4)		33 (4.4)	16 (4.8)
Secondary	196 (26.2)		196 (26.2)	88 (26.4)
University	518 (69.3)		518 (69.3)	229 (68.8)
Employment status		0 (0.0)		
Contract	630 (84.3)		630 (84.3)	273 (81.9)
No contract	117 (15.7)		117 (15.7)	60 (18.0)
Hospital		6 (0.8)		
Hospital A	314 (42.4)		317 (42.4)	105 (37.5)
Hospital B	54 (7.3)		55 (7.4)	58 (20.7)
Hospital C	314 (42.4)		316 (42.3)	91 (32.5)
Home/Other	59 (8.0)		59 (7.9)	26 (9.3)
Parity[a]		0 (0.0)		
nulliparous	449 (60.1)		449 (60.1)	208 (62.5)
1 child	237 (31.7)		237 (31.7)	94 (28.2)
2 or more	61 (8.2)		61 (8.2)	31 (9.3)
Body mass index (BMI)[b] **(kg/m2)**		59 (7.9)		
Underweight (< 18.5)	23 (3.3)		25 (3.4)	7 (2.2)
Normal (18.5 – < 25)	434 (63.0)		474 (63.5)	195 (62.5)
Overweight (≥25 – < 30)	166 (24.1)		176 (23.6)	75 (24.0)
Obese (≥ 30)	65 (9.4)		72 (9.6)	35 (11.2)
Pregnancy Pathologies				
No HDP	672 (96.8)		719 (96.2)	250 (75.0)
HDP[c]	22 (3.2)	53 (7.0)	28 (3.8)	13 (4.9)
No GD	662 (95)		709 (94.9)	252 (75.7)
Gestational Diabetes	34 (4.9)	51 (6.8)	38 (5.0)	13 (4.9)
Smoking during pregnancy		23 (3.1)		
None	666 (92.0)		686 (91.8)	266 (91.4)
Yes	58 (8.0)		61 (8.2)	25 (8.6)
Previous Breastfeeding (wks)	29.15 ± 53.4	0 (0.0)	29.1 ± 53.4	27.42 ± 56.6
Seafood Intake (g/day)	48.38 ± 41.5	132 (17.7)	47.8 ± 39.4	50.32 ± 31.6
Omega-3 supplement		390 (52.2)		
No	280 (78.4)		579 (77.5)	100 (79.4)
Yes	77 (21.6)		168 (22.5)	26 (4.8)
Offspring Characteristics				
Sex		0 (0.0)		
Female	381 (51.1)		381 (51.1)	129 (38.7)
Male	366 (48.9)		366 (48.9)	158 (61.3)
Gestational age (days)	278.43 ± 9.5	1 (0.1)	278.4 ± 9.5	275.63 ± 16.5
Weight at birth (g)	3305.73 ± 469.6	5 (0.7)	3304.4 ± 469.6	3236.93 ± 589.0
HC[d] **at birth (mm)**	348.9 ± 26.5	39 (5.2)	348.8 ± 26.6	344.11 ± 22.7

[a] completed 20 weeks,
[b] BMI at 12 weeks,
[c] Hypertensive disorder during pregnancy,
[d] Head circumference.

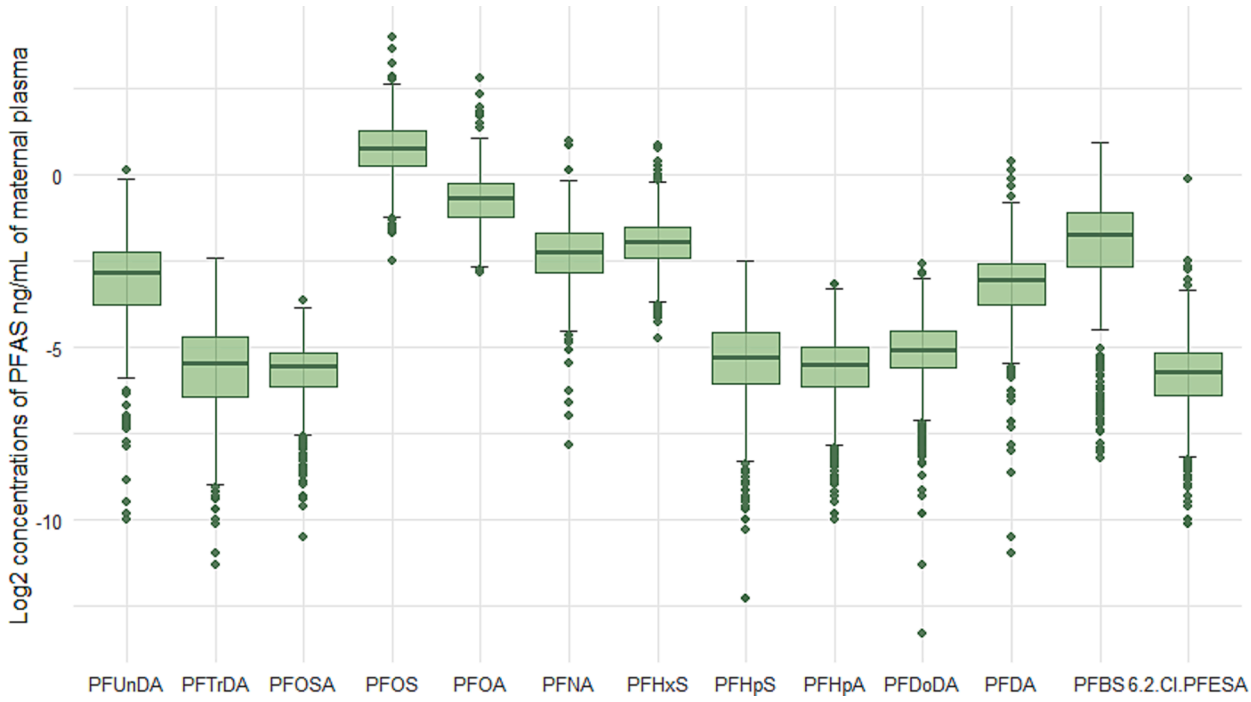

Fig. 1. Logarithm transformed (log_2) and imputed 'legacy' and 'next generation' per- and polyfluoroalkyl substances (PFAS) in maternal plasma at 32 weeks gestation.

highest concentrations (median 1.7, 0.63, 0.27 and 0.21 ng/mL, respectively). Other widely used PFAS, such as PFDA, and PFUnDA, also showed higher concentrations with > 97 % of sample values above the LOD (median 0.12, and 0.14 ng/mL, respectively). PFAS with lower concentrations included PFTrDA, PFHpS, and PFHpA (median 0.03, 0.03, 0.02 ng/mL, respectively). Regarding the next-generation PFAS, a high proportion of samples analyzed for 6.2.Cl.PFESA had concentrations above the detection limit > 88 % above LOD) but at lower levels

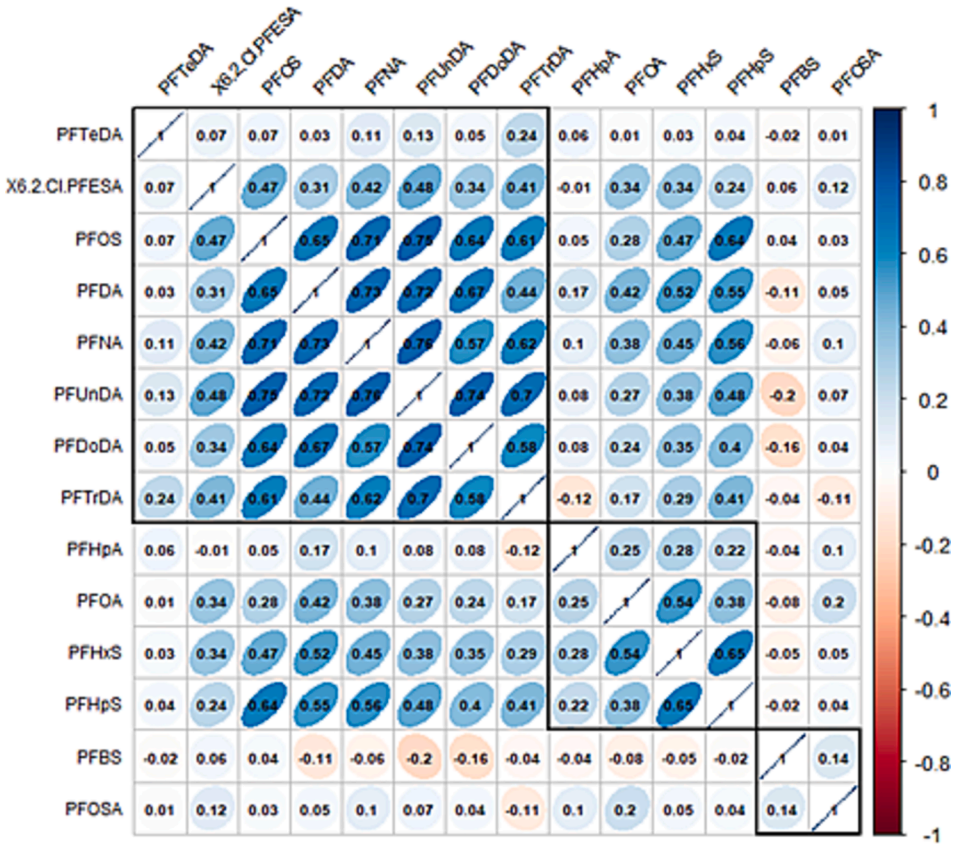

Fig. 2. Correlation heatmap using Pearson's correlation coefficients among the singular logarithm transformed (log_2) per- and polyfluoroalkyl substances (PFAS).

relative to the legacy PFAS (median 0.015 ng/mL).

Pearson's correlation heatmap revealed moderate to strong positive correlations among most of the 13 PFAS, with a tendency to correlate based on carbon chain length (Fig. 2). Hierarchical clusters revealed strong, positive correlations between PFOS, PFDA, PFNA, PFUnDA, and PFDoDa ($r > 0.7$), while PFHpA, PFOA, PFHxS, and PFHpS, were moderately correlated with each other and PFBS and PFOSA the least correlated with the other PFAS.

3.3. Prenatal per- and polyfluoroalkyl substances single exposure models

In the single chemical models, most PFAS exposures were associated with a decrease in fetal growth measurements AC, BPD, FL, HC and weight, although few associations demonstrated strong statistical evidence of association (Fig. 3, Table S5). For AC, a decrease in the mean standard score of 0.10 [95 % CI: −0.18, −0.02] and 0.06 [95 % CI: −0.11, −0.01], occurred in relation to a doubling in the concentration of PFOS and PFDoDa respectively. For BPD, we observed a decrease in mean standard score of 0.05 [95 % CI: −0.09, 0.00] associated with PFHpA exposure. A mean standard score increase of 0.05 [95 % CI: 0.00, 0.10] in FL was found for every doubling of PFOSA and a decrease in mean standard score by 0.04 [95 % CI: −0.08, 0.00] was associated with every doubling of PFHpS. We also observed a statistically significant decrease in HC associated with a doubling of PFOS, PFHxS, PFHpA, and PFDA (PFOS β = -0.10 [95 % CI: −0.18, −0.01], PFHxS β = -0.09 [95 % CI: −0.18, 0.00], PFHpA β = -0.05 [95 % CI: −0.09, 0.00], PFDA β = -0.06 [95 %CI: −0.12, 0.00], respectively). For fetal growth measured by weight (estimated and birth), PFOS, PFHpA, and PFDoDa were associated with a statistically significant decrease in mean standard score of weight (β PFOS = −0.13 [95 % CI: −0.22, −0.04], PFHpA β = -0.06 [95 %CI: −0.10, −0.01]; PFDoDa β = -0.05 [95 % CI: −0.10, 0.00]; respectively). Multiplying these changes in standard score by the standard deviation of birth weight in the study population (469.58 g), translates to a decrease in birth weight of approximately 61 g for PFOS, 28 g for PFHpA, and 24 g for PFDoDa exposure, respectively. For those PFAS that were also tested as tertiles, a decrease in fetal weight was observed with increasing exposure to the 3rd tertile of PFHpA (β = -0.18, [95 %CI: −0.34, −0.03]) and PFDA (β = -0.17 [95 %CI: −0.33, −0.01], and with fetal HC and 3rd tertile PFDA (β = -0.18 [95 %CI: −0.35, −0.02] (Table S6).

Most associations between singular PFAS and placental PI did not demonstrate strong statistical evidence of association (Fig. 4, Table S7), however the association between every doubling ng/mL of PFBS and increased CPR PI (β = 0.06 [95 % CI 0.01, 0.11]) was considered significant (Table S7). The remaining associations between CPR PI and singular PFAS showed a decrease in CPR PI with every doubling of ng/mL of singular PFAS exposure.

Regarding UmA PI, 11 PFAS were associated with a minimal increase in mean standard score of UmA PI (increased resistance) for every doubling of ng/mL of PFAS, except PFDA (β = 0.00 [95 % CI −0.04, 0.04]) and PFBS (β = -0.01 [95 % CI −0.03, 0.01]; an increase of UmA for every doubling of 6.2.Cl.PFESA (β = 0.04 [95 % CI 0.00, 0.08]) demonstrated weak statistical evidence of association (Table S7). For UtA PI, associations with singular PFAS showed a slight increase in mean standard score (increased arterial resistance) for 11 of the 13 PFAS measured. The remaining PFAS PFOA and PFHpA were associated with a decrease in UtA PI, indicating reduced resistance, though neither demonstrated strong statistically significant associations. For every doubling of PFUnDA, PFTrDA, PFDoDa, and PFDA stronger evidence for statistical association were observed with increases in PI values (increased resistance) (PFUnDA β = 0.08 [95 % CI: 0.00, 0.16], PFTrDA β = 0.07 [95 % CI: 0.01, 0.12]), PFDoDa β = 0.12 [95 % CI 0.05, 0.20]), PFDA (β = 0.10 [95 % CI 0.01, 0.19])(Table S7).

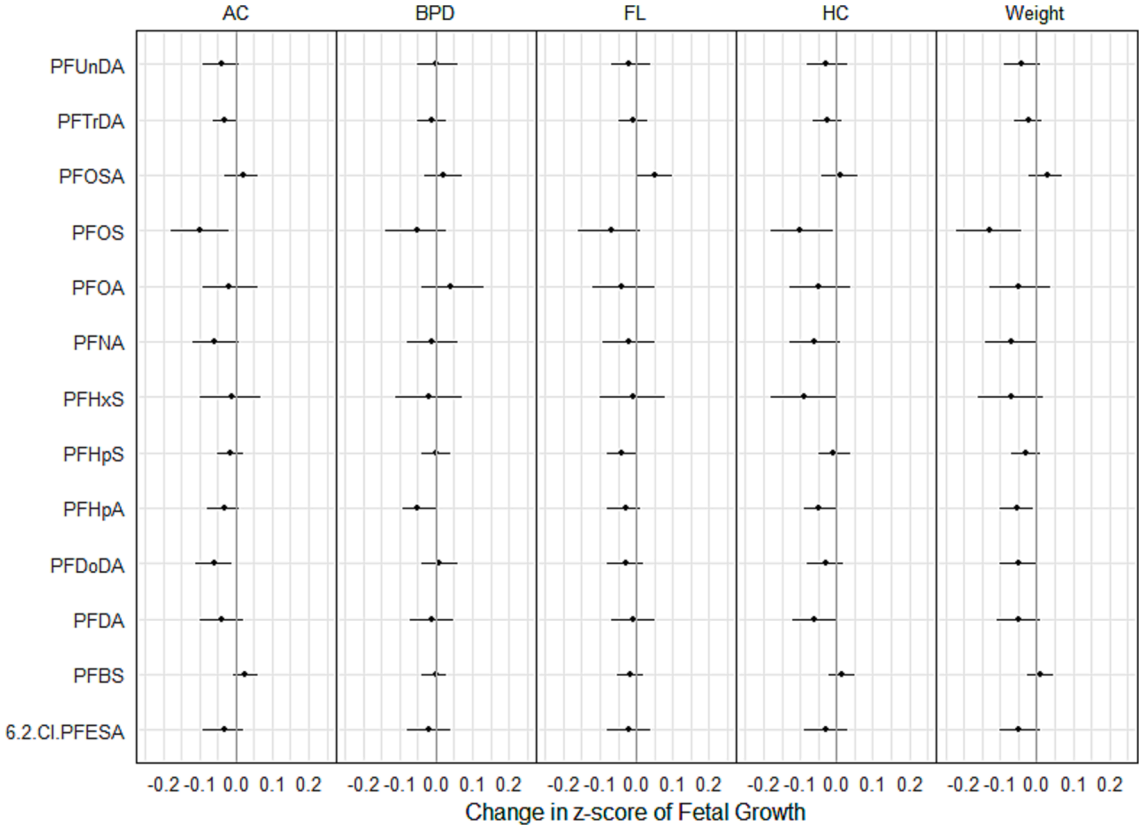

Fig. 3. Adjusted[a] associations (Beta and 95% CI) of fetal growth in pregnancy (z-score AC, BPD, FL) until birth (z-score HC, Weight) per doubling of single per- and polyfluoroalkyl exposures (ng/mL) in linear mixed models.

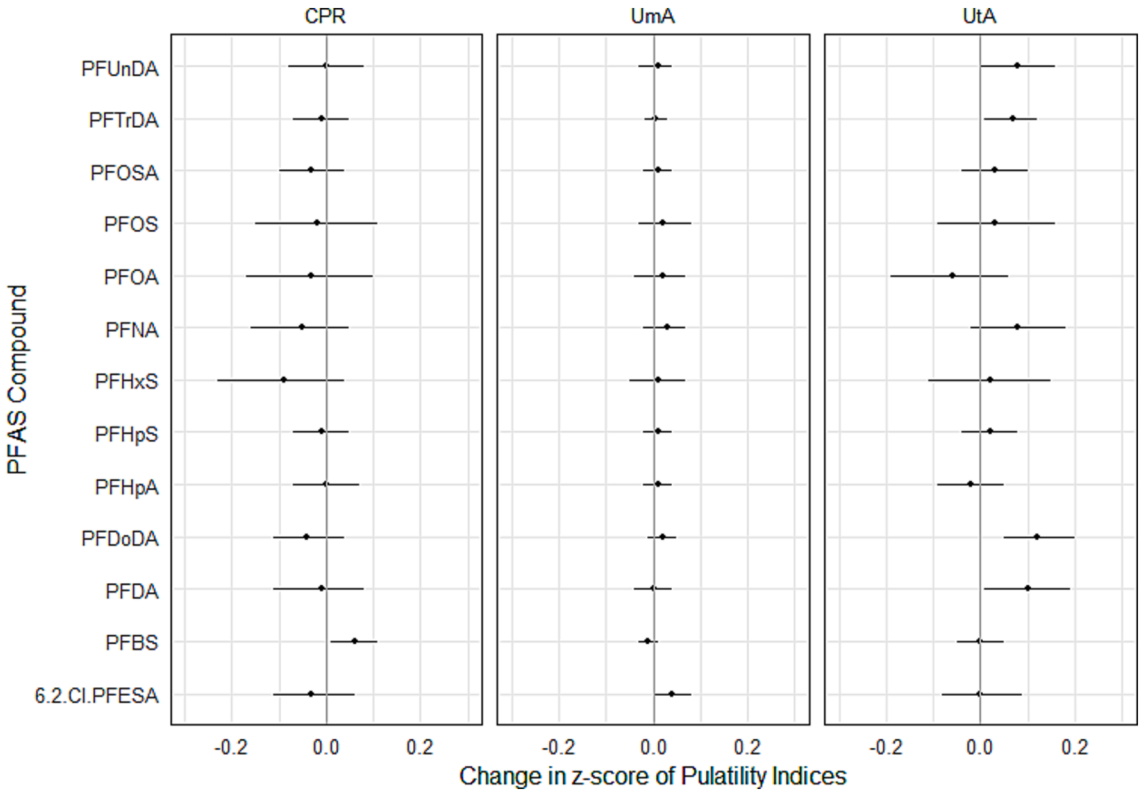

Fig. 4. Adjusted[a] associations (Beta and 95 % CI) of placental pulsatility indices (z-score CPR, UmA, UtA) at 32 weeks per doubling of single per- and polyfluoroalkyl exposures (ng/mL) in linear regression models.

3.4. Prenatal per- and polyfluoroalkyl substances mixture models

The BWQS models (Table 2) showed an overall decrease in fetal growth standard scores (AC, BPD, HC, FL) per increase in quartile mixture of PFAS at 32 weeks and 37 weeks; however, all credible intervals crossed zero, and were therefore not considered statistically significant. HC and weight at birth showed similar tendencies (HC β = -0.06 [CrI: −0.21, 0.08]; weight β = -0.09 [CrI: −0.22, 0.04]). PI values trended in the direction of values consistent with placental complications. A per quartile increase in the PFAS mixture was associated with a reduction in CPR, while a coherent increase in UmA and UtA were observed; however, little evidence of association was observed given that all credible intervals included zero. In all BWQS models, each singular PFAS contributed evenly to the mixture (weights 0.06–0.09) (Table S8).

3.5. Stratified analyses

In linear mixed models of fetal growth stratified by fetal sex, we again observed an overall tendency of reduction in fetal growth parameters for both female and male fetuses associated with every doubling of singular PFAS. Also, there was little statistical evidence for differences in associations between female and male fetuses (Table S9). In male fetuses, we observed a decrease in weight associated with PFTrDA exposure (β = -0.06 [95 % CI: −0.11, −0.00]), which was not observed in females (β = 0.01 [95 % CI: −0.038, 0.065) (p-interaction = 0.07). Similarly, in BWQS models there were little differences by fetal sex and there was no statistical evidence of interaction (Table S10). Stratification by time window (32– vs 37-weeks vs birth) revealed weak evidence of interaction with time window for PFOS, PFOS, and PFHxS for estimated fetal weight (Table S11). We found evidence that PFOS, PFOA, and PFHxS showed differing magnitudes of estimated effect on fetal weight across the time windows (PFOS: 32 weeks, β = -0.15 [95 % CI: −0.26, −0.04]; 37 weeks, β = -0.09 [95 % CI: −0.18, 0.00], birth, β

Table 2
Adjusted[a] associations (Beta and 95 % CrI) between fetal growth (z-score) at 32 and 37 weeks (AC, BPD, FL, HC, EFW), and birth (HC, weight) and pulsatility indices (z-score) at 32 weeks (CPR, UmA, UtA) per quartile increase of log_2-transformed per- and polyfluoroalkyl mixtures.

	32 weeks		37 weeks		Birth	
	β	95 % CrI	β	95 % CrI	β	95 % CrI
AC	−0.07	(−0.17, 0.04)	−0.05	(−0.16, 0.06)	–	–
BPD	−0.01	(−0.12, 0.11)	−0.01	(−0.14, 0.10)	–	–
FL	0.01	(−0.11, 0.13)	−0.12	(−0.25, 0.01)	–	–
HC	−0.00	(−0.11, 0.11)	−0.07	(−0.18, 0.06)	−0.06	(−0.21, 0.08)
EFW	−0.04	(−0.14, 0.08)	−0.08	(−0.21, 0.04)	−0.09	(−0.22, 0.04)
CPR	−0.04	(−0.20, 0.12)	–	–	–	–
UmA	0.03	(−0.04, 0.10)	–	–	–	–
UtA	0.01	(−0.05, 0.25)	–	–	–	–

[a] Models with fetal growth as the outcome were adjusted for maternal BMI at 12 weeks gestation (kg/m2) maternal education completed (primary, secondary, university), ethnicity (European, Latin American, Other), hospital, maternal age at 12 weeks of gestation (years), parity, seafood diet (grams/day), and smoking during pregnancy (no/yes). Models with pulsatility indices as the outcome were adjusted by BMI at 12 weeks gestation (kg/m^2), maternal age at 12 weeks of gestation, parity, hospital, seafood diet (grams/day) and smoking during pregnancy (none/yes). Using the first set (m = 1/20) of covariate imputed data and log_2-transformed concentrations of PFASs. Abbreviations: AC, abdominal circumference; BPD, biparietal diameter; FL, femur length; HC, head circumference; EFW, estimated fetal weight; CPR, cerebroplacental ratio; UmA, umbilical artery, UtA, uterine artery. CrI, credible interval.

= -0.11, [95 % CI: −0.21, −0.02], p-interaction = 0.10; PFOA: 32 weeks, β = -0.08 [95 % CI: −0.19, 0.03], 37 weeks, β = -0.03 [95 % CI: −0.12, 0.06]; birth, β = -0.03 [95 % CI: −0.12, 0.070]; PFHxS: 32 weeks, β = -0.15 [95 % CI: −0.26, −0.03], 37 weeks, β = 0.00 [95 % CI: 0.10, 0.09], birth β = -0.04 [95 % CI: −0.143, 0.057] p-interaction = 0.01) (Table S11). Lastly, when the linear models were performed in the population restricted to those without a diagnosis of any hypertensive disorder during pregnancy, results were close to identical to the full sample population models (Table S12).

4. Discussion

In this population-based birth cohort study, single and mixture PFAS tended to be associated with reduced fetal growth parameters, and associations with pulsatility indices were consistent with changes to fetoplacental hemodynamics; however, the majority of associations did not reach statistical significance. We observed a statistically significant decrease in fetal growth parameters with PFOSA, PFOS, PFHxS, PFHpS, PFHpA, PFDoDa, and PFDA exposure. For pulsatility indices, statistically significant associations were observed with PFUnDA, PFTrDA, PFDoDa, PFDA (UtA), PFBS (CPR) and 6.2.Cl.PFESA (UmA) exposure. BWQS mixture models showed no statistically significant associations with any of the outcomes assessed. There was little evidence to support differences in associations by fetal sex or time windows. To our knowledge, this is the first study to examine the associations of a wide range of legacy and next-generation PFAS and their mixtures with in-utero fetal growth biometry and fetoplacental hemodynamics in a birth cohort.

In the present study based on a recently recruited birth cohort, PFAS levels at 32 weeks gestation were detected at lower levels compared to older global (Li et al., 2021; Wikström et al., 2020; Callan et al., 2016; Mahfouz et al., 2023; Malm et al., 2023) and Spanish birth cohorts (Costa et al., 2019; Manzano-Salgado et al., 2017; Rovira et al., 2019; Haug et al., 2018), across which there was high heterogeneity. The median concentrations of widely used PFOS, PFOA, PFHxS, and PFNA in the present study were 1.7, 0.63, 0.27, and 0.21 ng/mL, respectively. A large, 2016–2018 Chinese cohort (n = 879) found higher mean levels (PFOS 4.3 ng/mL, PFOA 1.3 ng/mL, PFNA 0.43 ng/mL) save for PFHxS (0.15 ng/mL) in mothers' serum taken across gestation (mean 32 weeks, range 7–40) (Qin et al 2023). In the older Spanish INMA cohort, PFAS were measured in 1202 maternal plasma samples during the first trimester collected between 2003 and 2008 (Costa et al., 2019) mean values of PFOS, PFOA, PFHxS, and PFNA were 6.05 ng/mL, 2.35 ng/mL, 0.58 ng/mL, and 0.66 ng/mL, respectively, so considerably higher than the current study except PFHxS. Padula et al. analyzed PFAS measured mostly in the 2nd trimester from 11 US cohorts (years 1999–2019), totaling 3,339 mother child dyads, and found median levels in mothers still higher than, but more similar to, the current study (PFOS 2.8 ng/mL, PFOA 1.2 ng/mL, PFHxS 1.0 ng/mL, PFNA 0.4 ng/mL). Padula et al highlight the significant differences in PFAS levels spanning the last two decades, and show a sharp decrease in the median values for legacy PFOA, PFOS, PFNA, PFHxS, and PFDA (Padula et al., 2023). It is likely that differences across years and cohorts are due to variations in production and legislation of PFAS by year and country (Kashino et al., 2020; McAdam and Bell, 2023; Convention, 2024). For example, following restrictions on the widespread use and production of PFOS and PFOA, production of next-generation PFAS continues to increase, increasing the importance of studying next generation PFAS, as they become more prevalent in the environment (ECHA, 2023). Notably, we detected 6:2-Cl.PFESA in our study population, a compound restricted to production in China and rarely found in North American or European populations. In a Beijing cohort of limited sample size (n = 84), Li et al., found more than 100 times higher concentrations of 6:2Cl-PFESA (mean 2.58 ng/mL) than the current study (mean 0.02 ng/mL). This finding underscores the variability in PFAS levels across populations and the necessity to investigate a comprehensive list of PFAS despite local regulation or trends in production (ECHA, 2024; Brase et al., 2021).

Many studies report statistically significant associations between prenatal exposure to singular PFAS and decreased birth weight (Costa et al., 2019; Manzano-Salgado et al., 2017; Kashino et al., 2020; Wikström et al., 2020; Callan et al., 2016; Kaiser et al., 2023; Chen et al., 2021; Padula et al., 2023; Mahfouz et al., 2023), and results from systematic review and *meta*-analyses support these findings (Bach et al., 2015; Gui et al., 2022; Steenland et al., 2018; Lan et al., 2023). Padula et al.s aforementioned pooled cohort study found associations between the majority of legacy PFAS PFNA, PFDA, PFOA, PFHxS, and PFOS and birthweight (n = 3,339) (Padula et al., 2023). Similarly, a large (n = 1985) Japanese birth cohort used by Kashino et al., found a decrease in birth weight of 96.2 g per each log10 unit increase of PFNA and − 72.2 g per each log10 unit increase of PFDA (Kashino et al., 2020). Despite large sample sizes in studies by Padula et al. and Kashino et al., these maternal populations may not be generalized to European populations. Assessing fetal growth at several time points during pregnancy could yield a more precise understanding of the mechanistic effects of PFAS, but there are few studies that have investigated the effects of PFAS exposure on fetal biometry across pregnancy using direct ultrasound measurements, and they report inconsistent results (Costa et al., 2019; Sevelsted et al., 2022; Ouidir et al., 2020; Peterson et al., 2022). In the Spanish INMA cohort (N = 1220), no association was found between PFAS exposure (measured in the first trimester of pregnancy) and fetal growth parameters AC, BPD, FL, and HC across gestational weeks 12, 20 and 34 (Costa et al., 2019). A Danish cohort of 653 mother–child pairs found a statistically significant decrease in birthweight z-score with increasing PFOS and PFOA levels, respectively, but not when fetal growth was measured as the birth growth measure minus the ultrasound measurements (Sevelsted et al., 2022). Ouidir et al, in a US cohort of over 2000 subjects, analyzed 11 singular PFAS in first trimester samples and reported associations between PFDA exposure and femur length which varied in direction by race, but no associations were found for the other PFAS compounds (Ouidir et al., 2020). In a small US cohort (n = 335), mothers with detected PFOA concentrations had fetuses with decreased head circumference and biparietal diameter ultrasound measurements compared to those mothers with non-detected concentrations. In the aforementioned Spanish cohort, Costa et al. observed no overall associations between four PFAS and fetal growth across pregnancy, but did find that smoking modified the direction of the effect depending on the PFAS (negative association with PFOA and PFNA, and a positive association with PFHxS or PFOS) (Costa et al., 2019). In the current study, we were not able to examine the role of tobacco due to the very small proportion of smokers in the study sample.

Though the current study found no statistically significant associations between PFAS mixtures and fetoplacental hemodynamics or fetal growth outcomes, previous studies have detected associations using a mixture analysis. A nested-case control study of British female infants found that when mixture methods were applied, EtFOSAA, PFOA, and MeFOSAA contributed the most to the mixture, which was associated with a decreased head circumference at birth (Marks et al., 2021). Despite the small sample size (n = 313) and its restriction to female infants, of note is that single-chemical analyses were similar to the weighted quantile sum results. A larger US cohort (n = 876) also assessed singular PFAS and PFAS mixtures, and found that an increase in the PFAS mixture by one quartile was associated with slight reductions in birth weight z-scores, wherein the significant associations in singular linear models mirrored the weights in the mixture model as well (i.e., PFNA, PFOA, PFDeA, and PFUdA) (Eick et al., 2023). Svensonn et al. 2021 also found that a mixture of endocrine disrupting chemicals that included PFAS was associated with a decrease in birthweight in which PFOA and PFDA contributed significantly to the WQS index (Svensson et al., 2021). Our BWQS model results were similar to the results of the single exposure models (i.e., similar direction of associations), though all credible intervals included zero, and weights of each singular PFAS were unremarkable. Given the highly variable concentrations of singular

PFAS, it is possible that the BWQS model was unable to effectively estimate weights for each compound, and that the required power to detect the overall effect of the mixture was not reached in our study.

To our knowledge, we are the first to examine associations between prenatal PFAS and pulsatility indices of the placenta. These indices have been used previously to explore the impact of maternal air pollution on placental function (Cahuana-Bartra et al., 2022; Carvalho et al., 2016; Ouidir et al., 2021). Environmental endocrine disruptors may modulate the placenta's ability to respond to hormonal cues from the mother and fetus, and lead to maladaptive developmental programing and altered fetal growth. Pulsatility indices are a clinical tool used to assess potential disruption of placental function via fetoplacental hemodynamics. Pregnancy complications such as preeclampsia, believed to originate in the placenta, can threaten fetal wellbeing and prospective birth cohort studies support an association between prenatal PFAS exposure and various placenta related pregnancy complications such as preeclampsia (Hall et al., 2022; Huang et al., 2019; Yu et al., 2021). Even though we found few statistically significant associations with the pulsatility indices, our results for fetal growth and pulsatility measures are in the same 'clinical direction'. In the context of reduced fetal growth due to placental insufficiency, the increased PI in both the UtA and UmA indicate increased resistance in maternal and placental blood flow, while the CPR (ratio MCA to UmA) decreases, a phenomenon that has been associated with adverse perinatal outcomes and fetal distress, such as the fetal brain sparing effect by the decrease in resistance of the MCA (Shahinaj et al., 2010; Tian and Yang, 2022). Of the few statistically significant associations in the current study, increasing PFTrDA, PFDoDa, and PFDA were associated with an increase in z-score of UtA in the third trimester. Regarding UmA and CPR PI, despite that few associations reached statistical significance, the majority showed an increase in UmA PI (increased resistance to blood flow) and a decrease in the CPR PI (potential fetal distress). We note, however, that placental hemodynamics are complex and dynamic across pregnancy, especially when evaluating the risk of fetal growth restriction (Khalil et al., 2017). Therefore, repeated measurements of these parameters could provide a more comprehensive understanding of the potential effects of PFAS. Further research in population cohorts is necessary to fully understand the role of the placenta in fetal growth and how it may be affected by PFAS.

Several suggested mechanisms underline the associations between PFAS and fetal growth and placenta hemodynamics, including through epigenetic mechanisms and endocrine disruption. First, research suggests that PFAS exposure may trigger systemic inflammation or oxidative stress, contributing to altered placental gene expression, which may directly affect hormonal function. Kim et al., for example, found that several persistent organic pollutants (POPs) were associated with DNA methylation of the genes involved in thyroid hormone supply in the placenta (Kim et al., 2019). Second, due to their affinity for sex steroid, corticosteroid, and thyroid hormone receptors, PFAS could affect maternal fetoplacental signaling and cardiovascular adaptation required for a healthy pregnancy (Bloom et al., 2022; Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, et al. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocr Rev. 1 de diciembre de, 2015; Derakhshan et al., 2022; Toloza et al., 2022; Medici et al., 2014). Third, in tandem with disruptions in hormones, PFAS may alter lipid metabolism or disrupt the peroxisome proliferator-activated receptors (PPAR) signaling pathways (Szilagyi et al., 2020; Bloom et al., 2022; Dimasuay et al., 2016; Chan et al., 2009). PPARs regulate lipid and glucose metabolism and vascularization adaptations of the mother, which in turn regulate the nutritional requirements of the fetus (Szilagyi et al., 2020; Wieser et al., 2008). PFAS have been shown to disrupt PPARs pathways, influencing maternal thyroid function and lipid metabolism, which can lead to lower birth weight. For example, a birth cohort study found that most of the 14 PFAS examined were positively associated with an increased fetal-placental weight ratio, a marker of potential placental insufficiency. (Toloza et al., 2022; Conley et al., 2021; Yao et al., 2023). In addition to disruptions in the lipid signaling system, PFAS may also impact corticosteroid and reproductive hormones. For example, changes to gonadocorticoids or glucocorticoid hormone regulation, can lead to alterations in fetal programming and important metabolic pathways during development (Chang et al., 2022; Cai et al., 2023).

The present study has several strengths. First, the comprehensive list of PFAS assessed included the less studied, 'next-generation' PFAS in addition to well-studied 'legacy' PFAS (Convention, 2024). Given the thousands in production, it is increasingly important to examine a broad variety of PFAS. While some PFAS have been phased out, replacement compounds are now widely used, yet their safety remains uncertain. Differences in carbon chain length and persistence in the environment, in line with bioaccumulation potential may influence health outcomes (Kashino et al., 2020).

Results from our study emphasize the complementary benefit of examining both single and mixture exposures. Linear mixed single exposure models can quantify adverse health outcomes of a comprehensive list of PFAS in a direct and interpretable way, assessing longitudinal effects. In contrast, mixture models help to detect potentially cumulative or joint toxic effects of exposures, given the high likelihood that humans are exposed to a mixture of PFAS s at a time. One advantage of using BWQS in addition to linear mixed models is that BWQS models are able to detect associations in which the exposure mixture may have a non-linear relationship with fetal growth outcomes, and are not dependent upon directionality of associations.

Many studies have examined birth outcomes (SGA, LBW) in relation to environmental exposures, however, these outcomes can lack specificity to detect restricted fetal growth as most SGA neonates are healthy (Hutcheon et al., 2021). Furthermore, LBW is only measured at birth, failing to examine sensitive time windows and making comparison of fetal growth across populations difficult (Fetal, 2021). A key strength of our study is the assessment of fetal biometry during the third trimester, in which different pathological patterns of growth restriction may emerge (Fetal, 2021; Deter et al., 2018). Furthermore, our use of repeated measurements over time with linear mixed models allows us to detect deviations from normal growth patterns while accounting for individual differences.

Our study is not without limitations. Firstly, in the BiSC cohort maternal blood was sampled in the third trimester of pregnancy, which may not be the optimal time for assessment of PFAS exposure. It has been reported that serum detection of PFAS decreases as pregnancy progresses, with some variability between PFAS (Chen et al., 2021). The overall decrease is likely due to the physiological changes of increased glomerular filtration rates (GFR) and increased plasma volume, which can impact exposure assessments (Gui et al., 2022; Verner et al., 2015). Notably, GFR increases by 40–50 % as early as the first trimester and is sustained throughout pregnancy, while plasma volume peaks around 32 weeks (Vricella, 2017; Cheung and Renal, 2013; Lopes van Balen et al., 2019), and both potentially lead to increased excretion or dilution of PFAS in maternal blood. In turn, both may be associated with lower birth weight (Wikström et al., 2020; Salas et al., 2006). Adjustment for GFR has been suggested to account for these changes (Verner et al., 2015), but in the BiSC study markers for GFR were not available. Confounding by GFR may have inflated our effect estimates somewhat, as indicated by a *meta*-analysis that found that early blood sampling (i.e., first trimester) had little to no associations with lower birth weight when compared to blood sampled in the 3rd trimester (Steenland et al., 2018). However, studies by Costa et al. and Manzano-Salgado et al., which sampled PFAS during the first trimester, found that associations were not influenced by controlling for estimated GFR (Costa et al., 2019; Manzano-Salgado et al., 2017).

Although our study evaluated next-generation PFAS, which have similar chemical structure to legacy PFAS, it is possible that not enough time has passed for bioaccumulation of these emerging PFAS due to the varying half-lives. The overall levels of PFAS in our cohort was lower

than in other international birth cohorts (Costa et al., 2019; Manzano-Salgado et al., 2017; Kashino et al., 2020; Wikström et al., 2020; Callan et al., 2016; Kaiser et al., 2023; Chen et al., 2021; Padula et al., 2023; Mahfouz et al., 2023). Specifically, PFTrDA, PFOSA, PFHpS, PFHpA, and PFDoDa had significant proportions of samples below the limit of quantification and are therefore less reliable than values above the LOQ. Despite the relatively long half-lives of legacy PFAS, the assumption that similar levels persist from early pregnancy may not hold true for PFAS with shorter half-lives, such as PFBS (0.12 years) or PFHxA (1.63 years) (Brendel et al., 2018; Xu et al., 2020). In the context of low levels, it remains informative to measure continuous PFAS levels as opposed to dichotomization, given the possibility of a dose–response relationship. However, in this context, results should be interpreted with caution.

The testing of multiple comparisons is a limitation of our study, as is common in environmental epidemiology. However, given the lack of consensus on the threshold to correct for multiple testing (Sjölander and Vansteelandt, 2019), we compromised between the frequentist and Bayesian frameworks, examining consistencies between the models instead of applying restrictive corrections for multiple testing. This allowed a more qualitative, reasoned approach when interpreting our results.

Lastly, this study's source population was drawn from three hospitals, all located within the city of Barcelona, which may limit the generalizability of the findings. Barcelona is a diverse metropolitan area, wealthier neighborhoods experience higher levels of pollution due to the surrounding topography, thus this urban setting may not reflect conditions in other large cities or more rural regions. Additionally, the external validity of the study could be influenced by the higher education levels of the participants, as 69 % held university degrees, slightly more than the 64 % of women with degrees reported in Barcelona in 2019 (Dadvand et al, 2024).

5. Conclusion

This study was the first to evaluate an extensive list of both legacy and next-generation PFAS in relation to longitudinal fetal growth measurements and fetoplacental hemodynamics assessed by pulsatility indices. Results suggest that legacy PFAS are associated with reduced fetal growth, but associations for next-generation PFAS and for the PFAS mixture were less conclusive. Associations between PFAS and fetoplacental hemodynamics warrant further investigation. Future studies with larger sample size and longitudinal measures of pulsatility indices would improve the quality of evidence.

CRediT authorship contribution statement

Bethany Knox: Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Nuria Güil-Oumrait:** Writing – review & editing, Validation, Resources, Methodology. **Xavier Basagaña:** Writing – review & editing, Resources, Methodology, Data curation. **Dora Cserbik:** Writing – review & editing, Resources, Methodology, Data curation. **Payam Dadvand:** Resources, Project administration, Methodology. **Maria Foraster:** Writing – review & editing, Resources, Data curation. **Toni Galmes:** Validation, Software, Data curation. **Mireia Gascon:** Writing – review & editing, Resources, Project administration. **Maria Dolores Gómez-Roig:** Writing – review & editing, Resources, Data curation. **Laura Gómez-Herrera:** Validation, Resources. **Line Småstuen Haug:** Writing – review & editing, Validation, Resources, Methodology, Data curation. **Elisa Llurba:** Writing – review & editing, Resources, Methodology, Data curation. **Sandra Márquez:** Writing – review & editing, Software, Methodology. **Ioar Rivas:** Writing – review & editing, Resources, Project administration, Funding acquisition, Data curation. **Jordi Sunyer:** Writing – review & editing, Supervision, Project administration. **Cathrine Thomsen:** Writing – review & editing, Resources, Data curation. **Maria Julia Zanini:** Writing – review & editing, Resources, Data curation. **Mariona Bustamante:** Writing – review & editing, Resources, Methodology, Data curation. **Martine Vrijheid:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

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Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.109090.

Data availability

Data will be made available on request.

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Further reading

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