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Per- and polyfluoroalkyl substances (PFAS) and fetal growth: A nation-wide register-based study on PFAS in drinking water

Melle Säve-Söderbergh [a,b,*], Irina Gyllenhammar [a], Tessa Schillemans [b], Emelie Lindfeldt [a], Carolina Vogs [b,c], Carolina Donat-Vargas [b,d,e], Emma Halldin Ankarberg [a], Anders Glynn [c], Lutz Ahrens [f], Emilie Helte [b], Agneta Åkesson [b]

[a] Risk- and Benefit Assessment Department, Swedish Food Agency, Uppsala, Sweden
[b] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[c] Department of Biomedical Sciences and Veterinary Public Health, Swedish University of Agricultural Sciences (SLU), Uppsala, Sweden
[d] Barcelona Intitute for Global Health (ISGlobal), Barcelona, Spain
[e] CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
[f] Department of Aquatic Sciences and Assessment, Swedish University of Agricultural Sciences (SLU), Uppsala, Sweden

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ABSTRACT

Background: There is inconclusive evidence for an association between per- and polyfluoroalkyl substances (PFAS) and fetal growth.
Objectives: We conducted a nation-wide register-based cohort study to assess the associations of the estimated maternal exposure to the sum (PFAS4) of perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS) with birthweight as well as risk of small- (SGA) and large-for-gestational-age (LGA).
Materials and methods: We included all births in Sweden during 2012–2018 of mothers residing ≥ four years prior to *partus* in localities served by municipal drinking water where PFAS were measured in raw and drinking water. Using a one-compartment toxicokinetic model we estimated cumulative maternal blood levels of PFAS4 during pregnancy by linking residential history, municipal PFAS water concentration and year-specific background serum PFAS concentrations in Sweden. Individual birth outcomes and covariates were obtained via register linkage. Mean values and 95 % confidence intervals (CI) of β coefficients and odds ratios (OR) were estimated by linear and logistic regressions, respectively. Quantile g-computation regression was conducted to assess the impact of PFAS4 mixture.
Results: Among the 248,804 singleton newborns included, no overall association was observed for PFAS4 and birthweight or SGA. However, an association was seen for LGA, multivariable-adjusted OR 1.08 (95% CI: 1.01–1.16) when comparing the highest PFAS4 quartile to the lowest. These associations remained for mixture effect approach where all PFAS, except for PFOA, contributed with a positive weight.
Discussions: We observed an association of the sum of PFAS4 – especially PFOS – with increased risk of LGA, but not with SGA or birthweight. The limitations linked to the exposure assessment still require caution in the interpretation.

1. Introduction

Due to high chemical and thermal stability and water repellent properties, per- and polyfluoroalkyl substances (PFAS) have been used for half a century in industrial processes and in a variety of commercial products (Gluge et al., 2020) and are ubiquitously spread into the environment (Houde et al., 2006; Sunderland et al., 2019). As there has been high regional contamination of raw water sources by PFAS, drinking water has been identified as an important local source of exposure (Domingo and Nadal, 2019; Glynn et al., 2020a; Gyllenhammar et al., 2015; Johanson et al., 2023; Xu et al., 2021).

Several suggested toxicological pathways link PFAS to adverse effects on fetal development have been identified, including disruption of thyroid hormone homeostasis, interactions with membrane and nuclear

* Corresponding author at: Swedish Food Agency, Box 622, SE-751 26 Uppsala, Sweden.
E-mail address: melle.save-soderbergh@slv.se (M. Säve-Söderbergh).

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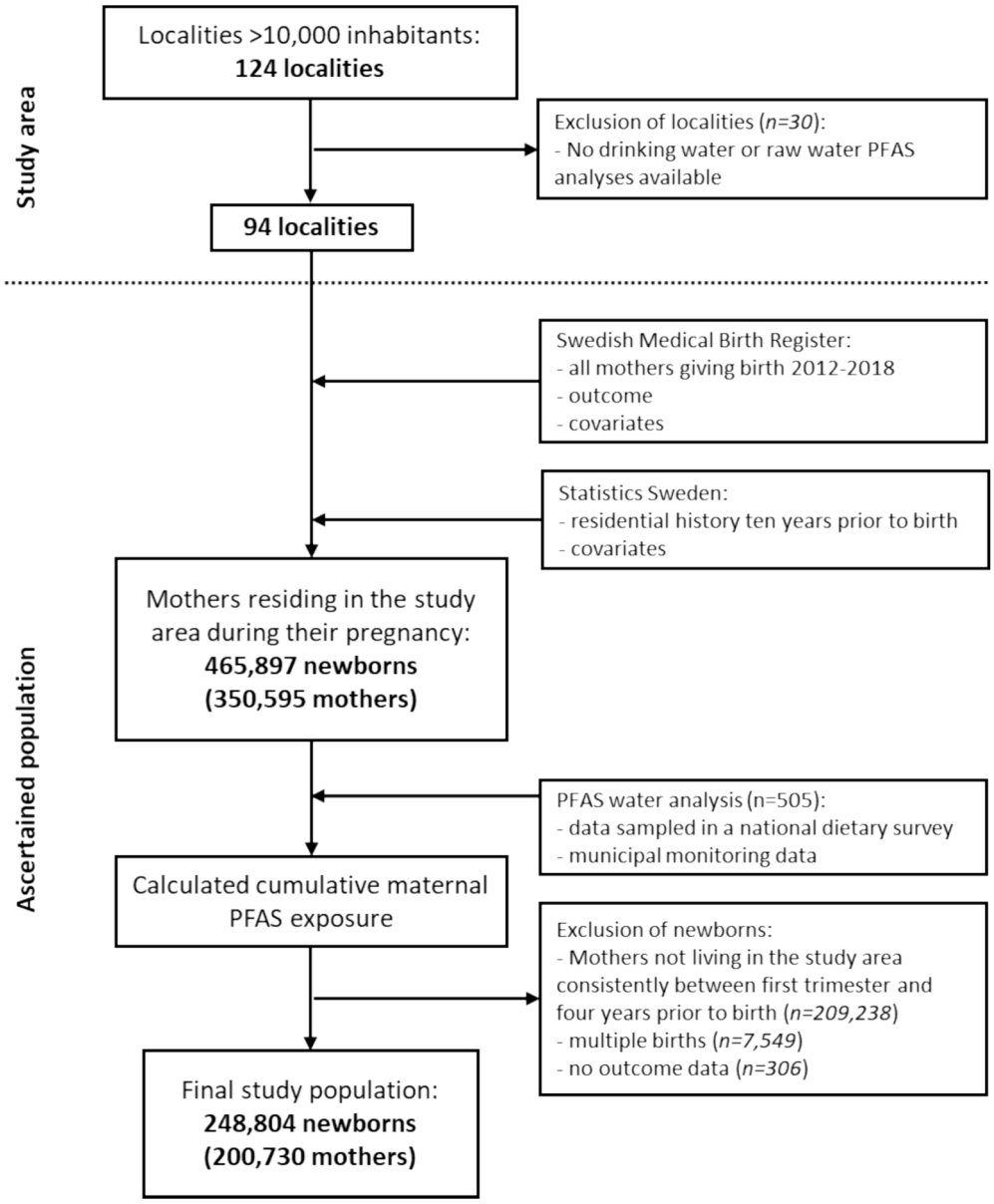


Fig. 1. Study area, study population and exposure of PFAS.

receptors, disruption of the estrogenic activity or disrupted placental function (Behr et al., 2018; Blake and Fenton, 2020; Gonzalez and Shah, 2008). Still, there are uncertainties about causality of associations that PFAS is associated with fetal growth (Knutsen et al., 2018; Schrenk et al., 2020; Steenland et al., 2018). In addition, confounding or reverse causality could potentially affect previous studies, due to variations in plasma volume expansion, glomerular filtration rate and albumin excretion that occur during the course of gestation (Cheung and Lafayette, 2013; Verner et al., 2015). On the other hand, no clear evidence is seen in studies using an ecological (i.e. community-level) exposure assessment, ignoring any physiological alterations during gestation (Engstrom et al., 2022; Manea et al., 2020; Waterfield et al., 2020; Zhu and Bartell, 2020). This considered, the inconclusive evidence of an association might still be due to inter-study differences in study populations and PFAS exposure levels.

As Sweden has extensive healthcare and administrative databases, as well as comprehensive data on PFAS in municipal raw and drinking water, we conducted a nation-wide register-based prospective cohort study on singletons born 2012–2018 in Sweden, using a locality-linked ecological exposure. We assessed the association between estimated cumulative maternal blood levels of the sum of four PFAS during pregnancy (calculated using a one-compartment toxicokinetic model and individually linked data on PFAS levels in the municipal drinking water supplying the participants) with birthweight and risk of being born small- (SGA) or large-for-gestational-age (LGA).

2. Materials and methods

2.1. Study area and population

We initially mapped all localities (coherent densely populated urban areas) in Sweden having a population of >10,000 inhabitants in 2015 (n = 124, representing about 60 % of the country's population) with respect to data on PFAS in raw (untreated) and drinking water (after treatment). This restriction on locality size ensured that the entire area received municipal drinking water, reducing the risk that parts of the population has received water from private wells. Of the 124 localities, we then had to exclude those localities – or parts of localities – lacking PFAS measurements in raw/drinking water for the municipal water works, resulting in the final inclusion of 94 localities in this study,

representing about 40 % of the country's population (Fig. 1). In cases where several water works supplied drinking water to the locality, the specific distribution areas were mapped for each water work using DeSO-codes (Demographic Statistics Areas) from the Geodatabase at Statistics Sweden, linking addresses to a specific drinking water distribution area only supplied by one water work. If distribution areas could not be separated due to mixing of water close to the outlet from two water works, the geometric mean of the two water works were used to estimate the PFAS exposure.

The study population was then identified as mothers giving birth between January 1st 2012 to December 31st 2018 (live or stillbirth) and having their official residential registration in one of the 94 localities at any time during their pregnancy. By selecting 2012–2018, when most of the PFAS drinking water analyses were performed, we were able to obtain an ample sample size of pregnant women without compromising the exposure information. In total, 465,897 newborns were included – of 350,595 mothers identified as living in the study area during their pregnancies (Fig. 1). To minimize misclassification of the internal maternal PFAS dose, we set *a priori* criterion that women should have resided at least four years prior to *partus* in any of our study areas to be included. The four years were chosen to be representative of the half-lives of most PFAS included in the study (Li et al., 2022; Yu et al., 2021). Following this criterion, we excluded 209,238 newborns. This considered, a reasonable number of participants were still included, avoiding influences of a limited sample size. Yet, we had residential data up to ten years prior to the birth, and if the women had lived within any of our selected localities for this longer time-period, this information was included and accounted for in the toxicokinetic model used to estimate the maternal exposure. Multiple births (i.e. ≥ twins) were also excluded (n = 7549 newborns).

Healthcare and administrative data were obtained for the mothers and newborns, by linking the maternal personal identification number (a unique identification number assigned to all Swedes), to Swedish Medical Birth Register at the National Board of Health and Welfare and the Longitudinal Integration Database for Health Insurance and Labour Market Studies at Statistics Sweden (Fig. 1). The study was approved by the Swedish Ethical Review Authority. Because the study was register-based, no informed consent was obtained for the data linkage.

2.2. Exposure assessment

A comprehensive database on municipal raw and drinking water PFAS concentrations was assembled from three different sources: (i) data sampled 2018 for a nationally representative dietary survey, Riksmaten Adolescence and analysed at the Swedish University of Agricultural Sciences (Glynn et al., 2020b), (ii) municipal monitoring data for 2014–2020, collected in a nation-wide survey in 2020 (Lindfeldt et al., 2021), analysed primarily at commercial laboratories, as well as (iii) data collected by personal communication with three water producers for PFAS levels measured before 2014 (i.e. high levels of PFAS and any changes in water production introduced related to this). In Glynn et al., (2020b), PFAS were analyzed in samples of drinking and raw water sampled twice (spring and autumn) during 2018 in six regions in Sweden, while the data from Lindfeldt et al. (2021), included PFAS sampled on average at six different occasions in raw and/or drinking water for each water work during 2014–2020. A total of 505 water analyses sampled in the study areas (305 raw water and 200 drinking water samples) were obtained, mostly sampled during 2018–2019, with at least one sample for each locality at any time point. We used the four most prevalent PFAS in drinking water and their sum PFAS4 (perfluorooctane sulfonic acid [PFOS], perfluorooctanoic acid [PFOA], perfluorononanoic acid [PFNA] and perfluorohexane sulfonic acid [PFHxS]) in this study, because the majority of the other individual PFAS concentrations were <limit of detection/quantification (LOD/LOQ) and contributed little or none to the final sum of PFAS (Table S1). For each PFAS, as well as the sum of PFAS4, we calculated the locality-specific average level of PFAS in water. We prioritized the use of PFAS measured in drinking water, but if not available, we also used PFAS measured in raw water. As it has been reported that most drinking water treatment methods currently used in the water treatment plants are inefficient to significantly reduce PFAS levels, and more efficient PFAS treatment methods – like reverse osmosis – are rare in Sweden, we assumed raw and drinking water PFAS levels to be comparable (Appleman et al., 2014). As improved analytical methods for PFAS have resulted in lower LOD/LOQ over time, measurements reported as either <LOQ or <LOD were treated as zero to reduce the risk of overestimating the exposure in areas where PFAS were measured in the early study period.

To best mirror the maternal PFAS exposure at individual level, we used a one-compartment toxicokinetic model to translate the exposure through drinking water to the cumulative maternal blood PFAS concentrations for the time of each individual pregnancy, Equation 1 (Bartell, 2017). In addition to considering the specific elimination rate constant of each PFAS, this model also accounts for the background PFAS exposure and maternal PFAS exposure through drinking water. The background PFAS exposure was obtained from two studies that measured serum PFAS in pregnant women in non-drinking water contaminated areas of Sweden considered to be representative; for PFOS and PFNA collected in 2002–2017 (Miaz et al., 2020), and PFOA and PFHxS collected in 2007–2010 (Shu et al., 2019). As mentioned, the drinking water PFAS was linked yearly up to maximum ten years prior to the birth (based on the information on the maternal address obtained for each year) given that the women lived within any of our study areas (one or more) throughout this period. In case of missing data on background PFAS concentrations for a specific year, we used the closest year available.

$$C_t = C_\infty + (C_0 - C_\infty) \times e^{-k*t}$$

where C_t is the serum PFAS concentration (ng/mL) for the specific year (t) at each individual pregnancy, C_∞ is the serum PFAS at steady state (ng/mL, from Eq. (2)), C_0 is the cumulative maternal serum PFAS concentration generated from previous years, based on exposure up to ten year prior to birth (ng/mL, the first year starting with the year-specific maternal background blood PFAS concentration as mentioned above (Miaz et al., 2020; Shu et al., 2019)), and k is the elimination rate constant determined as $\frac{\ln(2)}{T_{½}}$, where T½ is the half-life in years of each of the PFAS4 (females 15–50 years of age (Li et al., 2022): PFOS: 2.6, PFOA: 2.4, PFHxS: 4.5; females 20–55 years of age (Yu et al., 2021): PFNA: 3.4).

$$C_\infty = B + C_W \times \mathrm{SWR}$$

where B is the time-dependent (year-specific) maternal background blood PFAS concentration (ng/mL) as mentioned above (Miaz et al., 2020; Shu et al., 2019), C_W is the locality-specific average PFAS water concentration according to maternal residency each year, ten years prior to birth (ng/mL), SWR is the steady-state ratio of serum:water PFAS concentrations (PFOS: 34, PFOA: 43, PFNA: 78, PFHxS: 111 (Johanson et al., 2023)). The cumulative maternal serum levels (C_t) were calculated separately for each PFAS and then summed to PFAS4 as shown in Fig. S1. We categorized the obtained maternal PFAS4 into quartiles of the exposure distribution.

2.3. Outcomes and covariates

We used birthweight, SGA and LGA as the outcomes. Birthweight was defined as weight for gestational-age z-score according to WHO growth standards (Leroy, 2011). We collected data on SGA and LGA as registered at delivery care, *a priori* defined as <-2 (standard deviation (SD) or >+2 SD from the average weight at the gestational age and gender at *partus* (Marsal et al., 1996), respectively.

From the Swedish Medical Birth Register we also obtained information on maternal age, body mass index (BMI) at registration to antenatal care, smoking habits, parity and self-reported use of teratogenic drugs (class 3) (Nörby et al., 2013) as well as information on gender of the child. From Statistics Sweden we obtained data on country of birth, household income and highest attained education of the mother. Information on drinking water chlorination – a potential risk factor for SGA, that also may correlate with PFAS – was obtained from a previous study (Säve-Söderbergh et al., 2020).

2.4. Statistical analyses

Multivariable-adjusted linear regression was used to assess the association between estimated cumulative maternal blood levels of PFAS4 and the continuous outcome (birthweight), with results expressed as β coefficient and 95 % confidence intervals (CI). Multivariable-adjusted logistic regression was used for binary outcomes (SGA and LGA), with associations expressed as odds ratios (OR) and 95 % CI. Correlations between different PFAS were assessed using Spearman's correlation coefficient (rho). As parity and breast feeding is shown to reduce the maternal serum PFAS levels (Berg et al., 2014; Brantsaeter et al., 2013), and the background levels were obtained from studies on primigravida alone, we cannot exclude an overestimation and larger uncertainty in the estimated PFAS levels among multiparous women. Consequently, we stratified the analysis by nulliparous (n = 107,232) and multiparous women (n = 141,498). We also performed stratified analysis by gender of the child, as gender has been suggested to be a potential effect modifier of the association between PFAS and fetal growth (Engstrom et al., 2022; Wikstrom et al., 2020). The interactions were tested using the likelihood ratio test, comparing the models with and without interaction term (for interaction on the multiplicative scale).

To reduce dependency by siblings (more than one birth by the same mother during the study period), the intragroup correlation by mother was used in the regression analyses. Based on prior knowledge of potential risk factors for fetal growth and determinants of serum PFAS concentrations, we included in the multivariable-adjusted model maternal age (<25, 25-<30, 30-<35, 35-<40, ≥40 years), BMI (at registration to antenatal care: <18.5, 18.5-<25 25-<30, ≥30 kg/m^2), any use of teratogenic drugs (yes/no), smoking at registration to antenatal care (no smoking, 1–9 cigarettes/day, >9 cigarettes/day), mother's country of birth (categorized into Nordic/Europe/Africa/North and South America/Asia/other), highest attained education (elementary school/secondary education/post-secondary education), household income (yearly quartiles by year of birth) and use of hypochlorite in the municipal water treatment corresponding to their residences (yes/no).

To further explore the associations indicated to be significant, we plotted the data using restricted cubic splines with 3 knots of the distribution (at the 10th, 50th and 90th percentiles) (Orsini and Greenland, 2011). To reduce the impact from outliers (representing only one locality and one year) in the spline analysis, we included the first 99 % of the estimated PFAS4 levels. In parallel to the sum of PFAS4, we also assessed the associations of each individual PFAS, as well as the PFAS "mixture effect" using quantile g-computation regression with the qgcomp package (version 2.8.6) in R (Keil et al., 2020).

For all analysis, statistical significance level was set at ≤ 0.05 and all statistical analyses were performed using Stata 17.1 (StataCorp, Texas, USA) or R 3.6.1 (R Core Team).

3. Results

The estimated average cumulative maternal blood PFAS4 was 7.5 (SD: 2.5, interquartile range [IQR]: 6.8–8.2) ng/mL in blood. The average birthweight of the 248,804 singletons was 3,526 (SD: 555, IQR: 3,210–3,874) g, and 2.4 % (n = 6,001) and 3.3 % (n = 8,107) newborns were diagnosed as SGA and LGA, respectively. We generally observed a

Table 1
Baseline population characteristics among mothers giving birth in the study area in Sweden between 2012 and 2018, expressed as proportions of all included newborns (%) by quartiles (Q) of the estimated cumulative maternal exposure (ng/mL, based on a one-compartment toxicokinetic model) of the sum of PFAS4 (perfluorooctane sulfonic acid [PFOS], perfluorooctanoic acid [PFOA], perfluorononanoic acid [PFNA] and perfluorohexane sulfonic acid [PFHxS]).

Variables	Categories	Q1	Q2	Q3	Q4
Maternal PFAS4 ng/mL	mean (min–max)	6.6 (6.3–6.8)	7.1 (6.8–7.4)	7.8 (7.5–8.2)	9.5 (8.2–43)
Births included	N	64,698	59,881	62,399	62,132
Child characteristics					
Gender (%)	Girls	49	49	48	49
	Boys	51	51	52	51
Maternal characteristics					
Age (%)	<25 years	7	9	10	10
	25-<30 years	28	29	27	26
	30-<35 years	37	37	36	37
	35-<40 years	22	20	21	22
	>40 years	6	5	6	5
Body mass index (BMI) * (%)	<18.5	2	2	3	2
	18.5-<25	56	57	59	59
	25-<30	24	24	23	23
	≥30	13	12	12	10
	No data	5	4	4	5
Parity (%)	Nulliparous	44	43	42	43
	Multipara	56	57	58	57
Smoking* (%)	No smoking	89	92	92	92
	1–9 cig./day	3	4	4	4
	>9 cig./day	1	1	1	1
	No data	7	4	3	3
Birth region (%)	Nordic	75	72	72	71
	Europe	8	8	8	7
	Africa	5	6	6	6
	North and South America	2	2	2	2
	Asia	11	13	13	14
	other	<1	<1	<1	<1
Use of teratogenic drugs* (%)	No	97	98	98	99
	Yes	3	2	2	1
Highest attained educational level (%)	Elementary school	9	10	11	11
	Secondary education	32	32	32	32
	Post-secondary education or higher	59	58	57	57
Household income (quartiles by year of birth) (%)	1st quartile	23	19	15	12
	2nd quartile	29	29	25	17
	3rd quartile	24	27	31	32
	4th quartile	24	25	29	39

[a]As reported at registration to antenatal care.
Missing data: BMI (4%), smoking status (4%), birth region (1%) and educational level (1%).

Table 2
Multivariable-adjusted linear regression of birthweight by quartiles (Q) estimated cumulative maternal blood levels of PFAS4 (ng/mL, based on a one-compartment toxicokinetic model) expressed as β coefficient and 95 % confidence interval (CI). The study included 248,804 singletons born during 2012–2018 to mothers living in areas >10,000 inhabitants in Sweden where PFAS drinking water data was available.

Population	Category	Q1 OR	Q2 β 95 % CI	Q3 β 95 % CI	Q4 β 95 % CI	p-trend
Births included	n	64,650	59,793	62,339	62,022	
All (n = 248,730)	Crude	ref	−7.1 (-18 to 3.5)	−8.2 (-19 to 2.2)	−0.4 (-11 to 10)	
	Multivariable-adjusted	ref	1.2 (-10 to 13)	−0.6 (-12 to 11)	−4.3 (-18 to 9.2)	0.7
Nulliparous (n = 107,232)	Crude	ref	−11 (-27 to 5.0)	−26 (-43 to −10)	−2.6 (-19 to 13)	
	Multivariable-adjusted	ref	−2.8 (-20 to 15)	−12 (-30 to 5.6)	12 (-7.8 to 34)	0.6
Multiparous (n = 141,498)	Crude	ref	−10 (-24 to 3.6)	−5.9 (-19 to 7.6)	−3.8 (-17 to 9.8)	
	Multivariable-adjusted	ref	0.5 (-15 to 16)	2.4 (-13 to 17)	−7.8 (-26 to 10)	0.7
Girls (n = 120,841)	Crude	ref	−7.3 (−22 to 7.1)	−2.9 (−17 to 11)	1.1 (-13 to 15)	
	Multivariable-adjusted	ref	−4.8 (-20 to 11)	0.9 (-15 to 17)	−4.8 (–23 to 14)	0.7
Boys (n = 127,889)	Crude	ref	−7.8 (−23 to 7.4)	−11 (-26 to 3.7)	−3.7 (-19 to 11)	
	Multivariable-adjusted	ref	6.5 (-10 to 23)	−0.04 (-17 to 17)	−5.6 (-25 to 14)	0.8

PFAS4 = sum of perfluoroctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorhexane sulfonic acid (PFHxS). Multivariable-adjustment: maternal age, BMI (body mass index), any maternal use of teratogenic drugs, smoking at registration to the antenatal care, country of birth, highest attained education and household income, as well as use of hypochlorite in the water treatment.

small differences in baseline characteristics across PFAS4 quartiles, except for the household income, where women in the lowest exposure category also had the lowest income (Table 1). The correlations between the estimated maternal blood level pairs of PFNA-PFHxS and PFOA-PFNA were low (rho $\leq$ 0.10) – as opposed to the high correlations observed for the pairs PFOS-PFNA and PFOA-PFHxS (rho: 0.77 and 0.89, respectively) (Table S2).

After multivariable-adjustment, we found no associations between estimated maternal blood PFAS4 and birthweight, neither in the main (comparing the highest to the lowest quartile β −4.3, 95 % CI −18 to 9.2 g, p-trend 0.7) nor in the stratified analyses (Table 2). Likewise, comparing the highest estimated maternal blood PFAS4 quartile with lowest, the risk of SGA was close to null (OR 1.03 95 % CI: 0.95–1.12, p-trend: 0.2, Table 3) although a significant association was seen for SGA among multiparous women (OR 1.17 95 % CI: 1.02–1.33, p-trend: 0.03). For the individual PFAS, PFHxS was significantly inversely associated with birthweight (β −11, 95 % CI −21 to −0.2 g, p-trend: 0.04), while PFNA indicated a positive association (β 15, 95 % CI 3.6 to 27 g, p-trend: 0.09) (Table S3), while none of the individual PFAS was associated with higher odds of SGA (Table S4).

In contrast, we observed significant associations of higher estimated cumulative maternal blood PFAS4 with increased risk of LGA, corresponding to an OR of 1.08 (95 % CI 1.01–1.16, p-trend: 0.04), when comparing extreme quartiles (Table 3). The association seen for the extreme quartiles was larger among children of nulliparous (OR, 1.20; 95 % CI 1.05–1.38, p-trend: 0.05) than multiparous women and in the female offspring (OR, 1.16; 95 % CI 1.05–1.28, p-trend: 0.003) as compared to the male (p-value for interaction 0.7, and 0.4, respectively). In addition, the restricted cubic spline of the association between the estimated PFAS4 and LGA showed no signs of departure from linearity (Fig. 2). For the single PFAS, the estimated cumulative maternal blood concentrations of PFOS and PFNA, were associated with increased odds of LGA with multivariable-adjusted ORs of 1.10 (95 % CI: 1.02–1.17, p-trend: 0.02) and 1.10 (95 % CI: 1.03–1.18, p-trend: 0.06), respectively, while no associations were seen for PFOA and PFHxS (Table S4).

The overall interpretation of "mixture effect" analysis were similar as seen in the other analyses, where a borderline statistically significant association of PFAS4 mixture for LGA per each quartile increment in estimated maternal blood levels of PFAS mixture was OR 1.07 (95 % CI: 1.00–1.15, p-trend 0.05). All PFAS – except PFOA – contributed with a positive weight to the total effect (Fig. 3), indicating that all PFAS except PFOA drive the observed associations with LGA.

4. Discussion

In this nation-wide register-based cohort, including close to 250,000 singleton newborns of mothers living in areas with PFAS data available in municipal drinking water in Sweden, we assessed the estimated cumulative maternal serum PFAS4 exposure in relation to fetal growth. While no overall associations were seen for birthweight and SGA, the results indicated a linear dose-dependent association with an increased risk of LGA, which was also confirmed in the mixture effect model. The ORs of the associations were larger among children of nulliparous as compared to multiparous mothers and among girls than boys. These results remained for some individual PFAS, especially PFOS, which also became evident in the assessment of mixture effect.

Experimental animal studies consistently indicate that single PFOA and PFOS exposures are associated with reduced birth and fetal weight (Negri et al., 2017; Schrenk et al., 2020). Several toxicological pathways have been suggested for the indicated association with fetal growth, including disruption of thyroid hormone homeostasis, interactions with membrane and nuclear receptors like peroxisome proliferator-activated receptor (PPARα), disruption of the estrogenic activity or disrupted placental function (Behr et al., 2018; Blake and Fenton, 2020; Gonzalez and Shah, 2008). Still, the relevance for PFAS effects on human fetal growth remains unclear, due to interspecies differences in response or the possibility that effect-levels in animal studies may be at levels not relevant to human exposure (Behr et al., 2018; Blake and Fenton, 2020; Gonzalez and Shah, 2008).

As concluded in reviews by the European Food Safety Authority (EFSA) (Knutsen et al., 2018; Schrenk et al., 2020), most previous human studies assessing the impact of PFAS on fetal growth have indicated an association between maternal PFAS concentrations in serum/plasma and reduced fetal growth, especially for PFOS and PFOA. Still, there is no clear indication of an association (Bach et al., 2016; Bell et al., 2018; Gao et al., 2021; Govarts et al., 2018; Hamm et al., 2010; Manzano-Salgado et al., 2017; Whitworth et al., 2012). With the exception of more recent studies (Padula et al., 2023), the bulk of these studies are limited in sample size and in addition, differences in population characteristics and exposure may influence the findings.

Studies with an ecological approach on the other hand, based on PFAS levels in drinking water in combination with maternal address

Table 3
Multivariable-adjusted logistic regression of small (SGA) and large for gestational age (LGA) by quartiles (Q) estimated cumulative maternal blood levels of PFAS4 (ng/mL, based on a one-compartment toxicokinetic model) expressed as odds ratios (OR) and 95 % confidence interval (CI). The study included 248,804 singletons born during 2012–2018 to mothers living in areas >10,000 inhabitants in Sweden.

Population/outcome	Category	Total births	Q1 OR	Q2 OR (95 % CI)	Q3 OR (95 % CI)	Q4 OR (95 % CI)	p-trend
SGA							
All	Cases (n)	248,804	1529	1469	1551	1452	
	Non-cases (n)		63,121	58,324	60,788	60,570	
	Crude		1.00 (ref)	1.04 (0.97–1.12)	1.05 (0.98–1.13)	0.99 (0.92–1.06)	
	Multivariable-adjusted		1.00 (ref)	1.05 (0.98–1.13)	1.09 (1.01–1.17)	1.03 (0.95–1.12)	0.2
Nulliparous	Cases (n)	107,277	991	926	991	865	
	Non-cases (n)		27,696	24,769	25,092	25,947	
	Crude		1.00 (ref)	1.04 (0.95–1.14)	1.10 (1.01–1.21)	0.93 (0.85–1.02)	
	Multivariable-adjusted		1.00 (ref)	1.05 (0.96–1.15)	1.11 (1.01–1.22)	0.92 (0.83–1.02)	0.7
Multiparous	Cases (n)	141,527	538	543	560	587	
	Non-cases (n)		34,425	33,555	35,696	34,623	
	Crude		1.00 (ref)	1.07 (0.95–1.20)	1.03 (0.92–1.16)	1.12 (0.99–1.26)	
	Multivariable-adjusted		1.00 (ref)	1.08 (0.95–1.22)	1.07 (0.94–1.20)	1.17 (1.02–1.33)	0.03
Girls	Cases (n)	120,886	725	686	743	705	
	Non-cases (n)		30,686	28,460	29,285	29,596	
	Crude		1.00 (ref)	1.02 (0.92–1.13)	1.07 (0.97–1.19)	1.01 (0.91–1.12)	
	Multivariable-adjusted		1.00 (ref)	1.03 (0.93–1.15)	1.11 (1.00–1.23)	1.05 (0.93–1.18)	0.2
Boys	Cases (n)	127,918	804	783	808	747	
	Non-cases (n)		32,435	29,864	31,503	30,974	
	Crude		1.00 (ref)	1.06 (0.96–1.17)	1.03 (0.94–1.14)	0.97 (0.88–1.08)	
	Multivariable-adjusted		1.00 (ref)	1.07 (0.97–1.19)	1.07 (0.97–1.18)	1.01 (0.90–1.13)	0.5
LGA							
All	Cases (n)	248,804	2,087	1,913	2,016	2,091	
	Non-cases (n)		62,563	57,880	60,323	59,931	
	Crude		1.00 (ref)	0.99 (0.93–1.05)	1.00 (0.94–1.07)	1.05 (0.98–1.11)	
	Multivariable-adjusted		1.00 (ref)	1.01 (0.95–1.08)	1.03 (0.97–1.10)	1.08 (1.01–1.16)	0.04
Nulliparous	Cases (n)	107,277	540	461	439	511	
	Non-cases (n)		28,147	25,234	25,644	26,302	
	Crude		1.00 (ref)	0.95 (0.84–1.08)	0.89 (0.79–1.01)	1.01 (0.89–1.14)	
	Multivariable-adjusted		1.00 (ref)	1.01 (0.89–1.14)	0.98 (0.86–1.11)	1.20 (1.05–1.38)	0.0.05
Multiparous	Cases (n)	141,527	1,547	1,452	1,577	1,581	
	Non-cases (n)		34,416	32,646	34,679	33,629	
	Crude		1.00 (ref)	0.99 (0.92–1.06)	1.01 (0.94–1.09)	1.05 (0.97–1.12)	
	Multivariable-adjusted		1.00 (ref)	1.01 (0.94–1.09)	1.04 (0.96–1.11)	1.06 (0.98–1.15)	0.1
Girls	Cases (n)	120,886	989	974	995	1,060	
	Non-cases (n)		30,422	28,172	29,033	29,241	
	Crude		1.00 (ref)	1.06 (0.97–1.16)	1.05 (0.96–1.15)	1.12 (1.02–1.22)	
	Multivariable-adjusted		1.00 (ref)	1.09 (1.00–1.20)	1.09 (0.99–1.19)	1.16 (1.05–1.28)	0.003
Boys	Cases (n)	127,918	1,098	939	1,021	1,031	
	Non-cases (n)		32,141	29,708	31,290	30,690	
	Crude		1.00 (ref)	0.93 (0.85–1.01)	0.96 (0.88–1.04)	0.98 (0.90–1.07)	
	Multivariable-adjusted		1.00 (ref)	0.94 (0.96–1.03)	0.98 (0.90–1.07)	1.01 (0.92–1.12)	1.0

PFAS4 = sum of perfluoroctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorhexane sulfonic acid (PFHxS). Multivariable-adjustment: maternal age, BMI (body mass index), any maternal use of teratogenic drugs, smoking at registration to the antenatal care, country of birth, highest attained education and household income, as well as use of hypochlorite in the water treatment.

data as a proxy for PFAS exposure, are generally larger in size and performed as natural experiments – assessing either the impact before and after lowering the drinking water PFAS levels (Waterfield et al., 2020) – or by comparing area-specific drinking water PFAS exposure (Engstrom et al., 2022; Manea et al., 2020; Zhu and Bartell, 2020). A significant association with risk of low birthweight (<2500 g) was observed in areas of Minnesota with PFOS- and PFOA-contaminated drinking water before as compared to after introducing granular activated charcoal water filtration to reduced PFAS concentrations below the guidelines (OR 1.36, 95 % CI 1.25–1.48, n > 48,000) (Waterfield et al., 2020). In a nation-wide study in the US – comprising more than eight million births – the direction and magnitude of associations between PFAS concentrations in drinking water and average country-level birthweight (multiple-stratified by county, maternal age, bridged-race, education, smoking status and parity) varied by individual PFAS (Zhu and Bartell, 2020). Thus, while several PFAS were associated with reduced birthweight, PFOA was associated with higher birthweight, which is opposite to the findings in the present study. In an area in

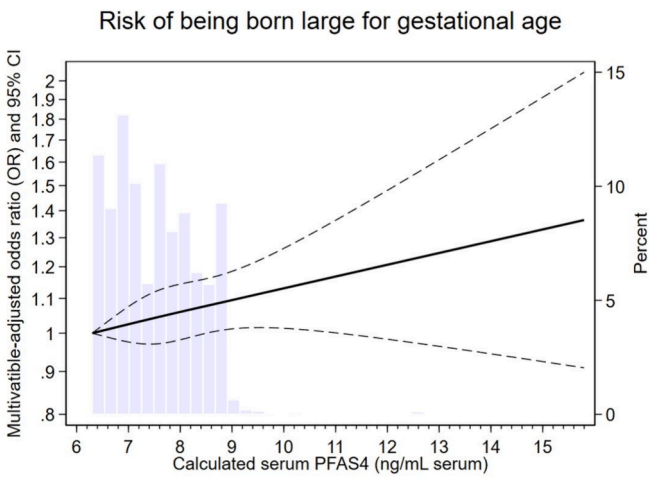
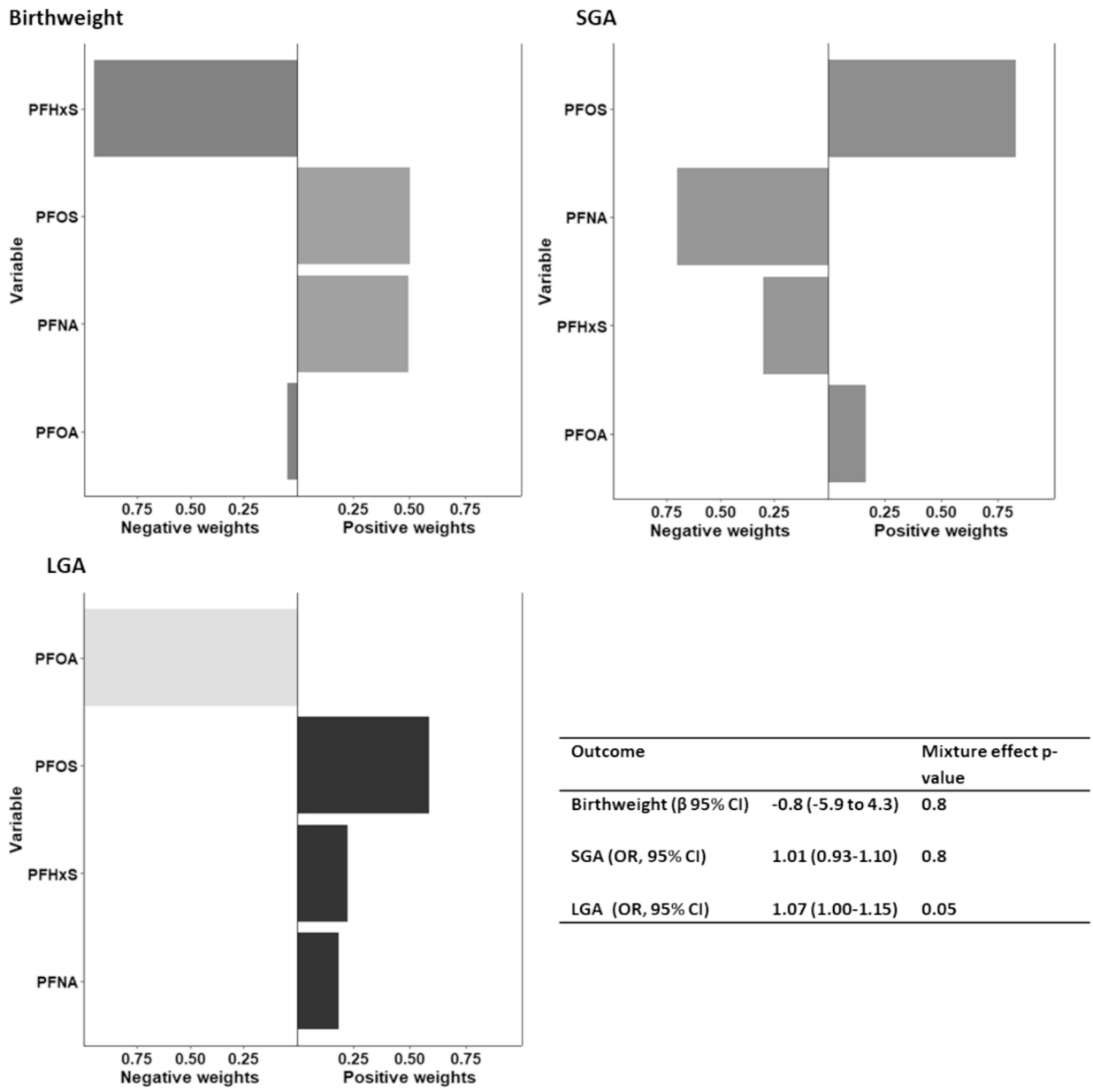


Fig. 2. Multivariable-adjusted odds ratios (OR) and 95% confidence intervals (CIs) of the first 99% of the estimated cumulative maternal blood levels of PFAS4 (ng/mL, based on a one-compartment toxicokinetic model) (sum of perfluorooctane sulfonic acid [PFOS], perfluorooctanoic acid [PFOA], perfluorononanoic acid [PFNA] and perfluorohexane sulfonic acid [PFHxS]) and the risk of large for gestational age (LGA) using restricted cubic splines with 3 knots of the distribution (at the 10th, 50th and 90th percentiles). Splines (solid line), 95% CIs (dashed lines) and the distribution of the estimated cumulative maternal exposure are illustrated in the histogram (blue bars). The study included of 248,804 singletons born during 2012–2018 in Sweden. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Sweden with highly contaminated drinking water (drinking water PFAS > 10,000 ng/L, especially PFOS and PFHxS), there was an indication for gender-specific associations with birthweight (Engstrom et al., 2022). The effect corresponding to a significant lower mean birthweight of 54 g (95 % CI −97 to −11 g) among boys and a significantly higher birthweight of 47 g (95 % CI 4 to 90 g) among girls being born in the high PFAS exposure area compared to the reference population from the surrounding counties (Engstrom et al., 2022). Engstrom et al. stated that although the biological mechanisms behind an association between PFAS and fetal growth is unknown, endocrine-disruptive properties may be involved, and sex steroids might be the reason behind the gender-related differences. Similar indications were found in the present study, as the risk of being born LGA was larger among girls, as compared to boys in the highest PFAS exposure group. In an Italian study from a highly contaminated area in Veneto Region (drinking water levels: PFOA 1,475 ng/L and PFOS 117 ng/L), PFAS was associated with increased risk of SGA (defined as < -3rd SD), multivariable-adjusted OR 1.27 (95 % CI 1.16–1.39), when compared to an un-contaminated area in the Veneto Region (Manea et al., 2020). Thus, even studies with a design resistant to physiological confounding, display corresponding inconsistencies in results. In any case, most previous studies point towards associations between PFAS and reduced fetal growth, which is only in line with our results for PFHxS. In Zhu and Bartell (2020) the PFAS-specific associations with fetal growth were predominantly inverse i.e., the higher the population-weighed PFAS the lower the birthweight. However, there were some exceptions that showed positive associations, which indicated that using the sum of PFAS can obscure potential PFAS-specific associations. While the present study indicated little evidence of an association with reduced fetal growth, it supports that a potential association between PFAS and fetal growth could be PFAS-specific.

Some limitations of the present study – especially linked to the exposure assessment – need to be addressed. While the use of an ecological exposure assessment has the benefit of being resistant to physiological confounding, this proxy of PFAS exposure does not account for variations in drinking tap water consumption, the use of bottled water or use of other drinking water sources due to e.g., commuting or seasonal migratory patterns. Also, we have no information on other sources of PFAS exposure, via food or the environment or variation in consumption pattern over the pregnancy. While this is a major limitation, great effort was made to adjust for the lack of PFAS exposure from other sources, by using year-specific maternal background blood PFAS concentration from pregnant women when estimating the exposure by the one-compartment toxicokinetic model. This considered, the estimation of the maternal background blood PFOA and PFHxS levels were based on samples collected 2007–2010 (Shu et al., 2019), and not throughout the whole study period, as was the case for PFOS and PFNA. This may have introduced some exposure misclassification, but considered to be the best option, since those samples represented non-contaminated areas in Sweden and there were support that blood levels of PFOA and PFHxS did not decline after 2010 in a similar manner as seen for other PFAS (Donat-Vargas et al., 2019), but were rather levelling out (Sonnenberg et al., 2023). In any case, the exposure misclassification is likely non-differential potentially attenuating the observed associations. At modestly elevated levels of PFAS in drinking water, however, drinking water PFAS may only contribute to a limited extent of the total exposure, potentially introducing exposure misclassification that needs to be considered when interpreting the findings. The exposure data of PFAS has some limitations, however, due to the extensive study population and fairly common outcomes, the misclassification of the exposure will be of less concern in the present study compared to studies with a small number of participants. Due to a limited number of PFAS water samples from several monitoring programs (n = 505) and by using a single PFAS exposure for each locality, fluctuations in the PFAS tap water levels may not be fully considered in our exposure estimates. In addition, the half-life of each PFAS plays a key role when estimating the cumulative maternal exposure. Due to large variations in reported half-lives, there is a risk that the PFAS levels calculated using the one-compartment model, may to some extent not reflect the actual maternal serum PFAS levels in the study population. Still, to reduce this risk, we used PFAS half-lives estimated from serum levels measured in a Swedish population. Here, a Monte Carlo approach could potentially be integrated in the toxicokinetic model to estimate variation in maternal PFAS serum concentrations. Yet, considering these limitations, we still made strong efforts to estimate the exposure accurately, using long term residential mobility pattern for each mother when calculating drinking water related PFAS exposure and adjusting for changes in PFAS serum background exposure over time. Moreover, only participants that received municipal drinking water were included in the study (excluding rural areas with private wells) and past changes in the drinking water treatment affecting the PFAS levels were accounted for. It should also be mentioned that a recent study indicated that the vast majority of the adult Swedish population consume drinking water from the tap (99.8 %). Most of the tap water is being consumed at home, and- the average water consumption including that in hot and cold foods and drinks is 2 L/day, and that the use of bottled water is very low (Säve-Söderbergh et al., 2018). In addition, when we estimated the cumulative maternal serum levels of PFAS, we used measured background PFAS serum levels sampled among pregnant Swedish women during the corresponding year as far back as 2002. It is expected that maternal serum PFAS levels are reduced as a result of parity and breastfeeding. To account for this slightly higher uncertainty in the estimated maternal PFAS in multiparous women than nulliparous women, we also stratified the analysis by parity. The results pointed towards a positive relation with LGA among nulliparous women alone, which aligns with the decreasing maternal PFAS concentrations with increasing parity (Berg et al., 2014).

Despite the shortcomings linked to the exposure assessment and the locality-linked ecological exposure, the present study has several important strengths that also need to be highlighted. This is one of the largest ecological studies using the data on PFAS exposure based on a comprehensive database on municipal raw and drinking water PFAS



Outcome		Mixture effect p-value
Birthweight (β 95% CI)	-0.8 (-5.9 to 4.3)	0.8
SGA (OR, 95% CI)	1.01 (0.93-1.10)	0.8
LGA (OR, 95% CI)	1.07 (1.00-1.15)	0.05

Fig. 3. Multivariable-adjusted quantile g-computation model of estimated maternal PFAS and change in birthweight, small (SGA) and large for gestational age (LGA), based on 248,804 singletons born during 2012–2018 in Sweden. The weights of the bars represent the proportion of the positive or negative partial effect for perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS) expressed as the β coefficient, odds ratios (OR) and 95% confidence interval (CI) of the mixture of the sum of PFAS4. The length of the bars corresponds to the effect size relative to the others in the same direction, while he darkness of the bars corresponds to the overall effect size, where increasing darkness indicating a larger effect. The table shows the odds ratio per one quartile increment in PFAS4. Multivariable-adjustment: maternal age, BMI (body mass index), any maternal use of teratogenic drugs, smoking at registration to the antenatal care, country of birth, highest attained education and household income, as well as use of hypochlorite in the water treatment.

concentrations and the prospectively collected data of fetal growth, including a large part of all Swedish children born during the seven-year study period. Although some data in the study was based on self-reported information from the registers – like smoking – most data came from health care or governmental administrative databases. In addition, the registers have a high coverage, close to 100 % of all completed pregnancies in Sweden (Källén and Källén, 2003; Ludvigsson et al., 2016), which is due to decades of publicly funded antenatal and delivery care in Sweden and compulsory reporting into the registers. The register-based design improved information reliability since only limited data were based on self-report and reduced the risk of most bias associated with recruitment of participants. In the present study, we used ±2 SD as cut-off for SGA and LGA, which is a more stringent cut-off than the 10th percentile commonly used, but by capturing mainly moderate to severe cases we improved the specificity. Due to the extensive information available in the Medical Birth Register, we were able to adjust for most relevant individual confounders. Still, despite our efforts to adjust for contextual confounding, by multi-level adjustment for regional differences in socioeconomics, we cannot fully exclude residual or locality-specific contextual confounding.

In conclusion, we observed an association of the sum of PFAS4 – especially PFOS – with increased risk of LGA, but not with SGA or birthweight. The limitations linked to the exposure assessment still require caution in the interpretation.

CRediT authorship contribution statement

Melle Säve-Söderbergh: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing - original draft. **Irina Gyllenhammar:** Conceptualization, Writing - review & editing. **Tessa Schillemans:** Methodology, Writing - review & editing. **Emelie Lindfeldt:** Data curation, Writing - review & editing. **Carolina Vogs:** Methodology, Writing - review & editin. **Carolina Donat-Vargas:** Methodology, Writing - review & editing. **Emma Halldin Ankarberg:** Conceptualization, Writing - review & editing. **Anders Glynn:** Conceptualization, Methodology, Writing - review & editing. **Lutz Ahrens:** Data curation, Writing - review & editing. **Emilie Helte:** Writing - review & editing. **Agneta Åkesson:** Conceptualization, Funding acquisition, Resources, Writing - review & editing.

Declaration of competing interest

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

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.108727.

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