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# Fetal exposure to perfluoroalkyl substances (PFAS) in drinking water and congenital malformations: A nation-wide register-based study on PFAS in drinking water

Melle Säve-Söderbergh [a,b,*,1], 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 Institute 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:* Teratogenic properties of perfluoroalkyl substances (PFAS) have been assessed in a few studies, however, epidemiological evidence for an association is inconclusive.
*Objectives:* We conducted a Swedish nation-wide register-based cohort study to assess the associations of estimated fetal exposure to the sum of drinking water perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS) with major congenital malformations.
*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 concentrations have been measured in drinking water. We estimated the fetal PFAS4 exposure by using a one-compartment toxicokinetic model – including maternal residential history, municipal PFAS water concentration and year-specific PFAS maternal background concentrations as input data – and accounting thereafter PFAS-specific transplacental transfer factors to estimate the fetal PFAS4 exposure. By register linkage we obtained birth outcomes and covariates. Odd ratios (OR) and 95 % confidence intervals (CI) of the associations between estimated PFAS in foetuses and major congenital malformations were estimated by logistic regressions and, complementary, by quantile g-computation regression for mixture effects.
*Results:* Analyses of 256,659 newborns of which 5,357 were diagnosed with major congenital malformations, revealed associations between fetal PFAS4 exposure and malformations on the nervous system OR, 2.84 (95 % CI: 1.38–5.84, p-trend: 0.008) and chromosomal anomalies OR, 1.50 (95 % CI: 1.07–2.10, p-trend: 0.009) comparing extreme quartiles. For the individual PFAS and in the quantile g-computation model, there were indications of an association between PFAS and urinary defects, OR 1.96 (95 % CI: 1.59–2.43, p-trend mixed effect: <0.001), primarily driven by PFOA and PFHxS.
*Discussion:* Modelled fetal sum of PFAS4 was associated with malformations of the nervous system and chromosomal anomalies, while the mixture assessment revealed associations with defects on urinary system. As the underlying toxicological mechanisms remains unclear, further investigation is warranted.

* Corresponding author at: Swedish Food Agency, Box 622, SE-751 26 Uppsala, Sweden.
*E-mail address:* melle.save-soderbergh@slv.se (M. Säve-Söderbergh).
[1] Present address: Institute of Environmental Medicine, Nobels väg 13, 171 65 Solna, Sweden.

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## 1. Introduction

For about half a century, perfluoralkyl substances (PFAS) have been used in industrial processes and in a variety of commercial products (Gluge et al. 2020; Houde et al. 2006), resulting in exposure from food, personal care, cleaning products, inhalation of PFAS in particulate matter outdoors or indoor from dust/aerosols, etc. PFAS have water repellent properties and high chemical and thermal stability with some PFAS also having long human half-lives (Li et al. 2022; Yu et al. 2021). Industrial emissions and the intense use of firefighting foam have generated PFAS hotspots worldwide, which have resulted in high PFAS levels in drinking water and blood plasma/serum in cumulatively exposed adult populations in these areas (Domingo and Nadal 2019; Glynn et al. 2020; Gyllenhammar et al. 2015; Johanson et al. 2023; Xu et al. 2021a). In Sweden, where PFAS exposure sources have been well studied, levels among adolescence may be already elevated above background when municipal drinking water PFAS have exceeded 2 ng/L (Nyström-Kandola et al. 2023). As these levels have consistently been reported in municipal drinking water in Sweden, even in large metropolitan areas (Lindfeldt et al. 2021), drinking water is considered an important contributor to the total PFAS exposure in Sweden, especially in highly contaminated areas (Xu et al. 2021b).

Some PFAS have been suggested to be associated with several adverse outcomes – including cancer, impaired immune function, metabolic perturbations, and neurodevelopmental defects – but for most outcomes the epidemiological evidence remains inconsistent (Sunderland et al. 2019). Although there is limited evidence of PFAS teratogenicity from experimental animal studies (DeWitt 2015), some epidemiological studies have pointed towards a possible association between PFAS exposure during the fetal development and major congenital malformations (Luo et al. 2022; Nolan et al. 2010; Ou et al. 2021; Savitz et al. 2012; Stein et al. 2009; Stein et al. 2014), especially craniofacial (Luo et al. 2022), brain (Stein et al. 2014) and heart defects (Ou et al. 2021). Still, several epidemiological studies indicated no association (Nolan et al. 2010; Savitz et al. 2012; Stein et al. 2009; Stein et al. 2014). Limited power in several previous studies, due to small sample size together with a rare outcome, urge the need for large-scale studies with relevant exposure contrast to explore a potential association.

We conducted a nation-wide register-based prospective study focusing on newborns, born 2012–2018 in Sweden, to assess the associations between modelled fetal PFAS4 (sum of perfluorooctanoic acid [PFOA], perfluorononanoic acid [PFNA], perfluorohexane sulfonic acid [PFHXs] and perfluorooctane sulfonic acid [PFOS]) exposure from drinking water (via one-compartment toxicokinetic modelling) and the risk of major congenital malformations.

## 2. Methods

### 2.1. Study area and population

The study methods have been described previously in (Säve-Söderbergh et al. 2024). Briefly, we identified the study area by localities (coherent and densely populated urban areas used for administrative division) in Sweden with a population of >10,000 inhabitants in 2015 (n = 124, representing about 60 % of the country's population). This means that some PFAS hotspot areas – like Ronneby (Xu et al. 2021b) – were not included due to their smaller population size. Of these, 30 localities – or parts of localities – were excluded due to lack of PFAS4 drinking water data. DeSO-codes (Demographic Statistics Areas) from the Geodatabase at Statistics Sweden were used to link mother's addresses to a specific drinking water distribution area exclusively supplied by one water work. If it was not feasible to differentiate distribution areas due to water blending near the outlets of two water works, the geometrical mean PFAS level from both was used to estimate the PFAS exposure. We selected 2012 to 2018 as our study period, because most of the PFAS drinking water analyses had been performed during this period.

We, thus, included all mothers giving birth between January 1st of 2012 to December 31st of 2018 (live or stillbirth) and residing in one of the 94 included localities during their pregnancy. This resulted in 465,897 newborns (singleton and multiple births) of 350,595 mothers (Fig. 1). To minimize the exposure misclassification of the individual PFAS drinking water dose, we further refined the analysis by requiring a minimum maternal residency period of at least four years before childbirth, leading to the exclusion of 209,238 newborns. A four-year period was chosen as it largely covers the half-lives (2.4–4.6 years) of the included PFAS (Li et al. 2022; Yu et al. 2021). However, for the included women we used residential data up to ten years prior to birth to estimate the maternal/fetal PFAS dose, increasing the robustness of the exposure estimations. During the period >4 to 10 years prior to each birth, only 7 % of the women had their residential address outside of the study area and were then assigned to the same information as for their first 4 years preceding the birth.

Health care, administrative and residential history data for the mother and newborns, were obtained by linking the maternal personal identification number (a unique identification number assigned to all Swedish residents), to the Swedish Medical Birth Register at the National Board of Health and Welfare (NBHW), the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) and Geodatabase at Statistics Sweden (Fig. 1). The study was approved by the Swedish Ethical Review Authority. Since the study was only register-based, no informed consent was obtained for persons included in the data linkage.

### 2.2. Exposure assessment

We obtained in total, 505 PFAS water analyses sampled within the study area (305 untreated raw water and 200 drinking water samples). Data was collected from three different sources. First, a nationally representative dietary survey, Riksmaten Adolescence in which samples were taken twice (spring and autumn) for each water work in 2018 and analysed at the Swedish University of Agricultural Sciences (Nyström-Kandola et al. 2023), resulting in a total of 58 samples. Second, municipal monitoring data sampled in 2014–2020 and collected in a nation-wide survey in 2020 (Lindfeldt et al. 2021), sampled during several seasons and analysed primarily at commercial laboratories, resulted in a total of 447 samples. Last, data collected by personal communication with three drinking water producers for PFAS levels measured before 2014 analysed primarily at commercial laboratories (i.e. where high levels of PFAS were detected and any consequences in the water production related to this that had to be accounted for in our modelling), resulting in summary PFAS levels for these three specific localities. The concentrations of the four most prevalent PFAS – PFOA, PFNA, PFHxS and PFOS – and their sum PFAS4 were used, as the majority of the other individual PFAS concentrations were <limit of detection/quantification (LOD/LOQ). Supplemental Table S1, shows the sampling frequency and summary of all the water PFAS concentrations assigned to each locality. We also obtained information directly from the producers, on any change in drinking water treatment (potentially affecting drinking water PFAS) throughout the study period and in case major changes in the drinking water production were maid that could have affected the PFAS concentrations (only relevant for three localities), this was accounted for. For each PFAS, as well as the sum of PFAS4, we calculated the locality-specific average PFAS exposure via drinking water. In the PFAS municipal monitoring programmes, raw water sampling was often prioritized over drinking water. Herein, we used both sources to estimate the exposure concentrations because raw water was considered a good approximation of the tap water PFAS concentrations, since most current drinking water treatment methods in the study area are ineffective in reducing the PFAS content (Appleman et al. 2014), as compared to granular activated carbon, reverse osmosis

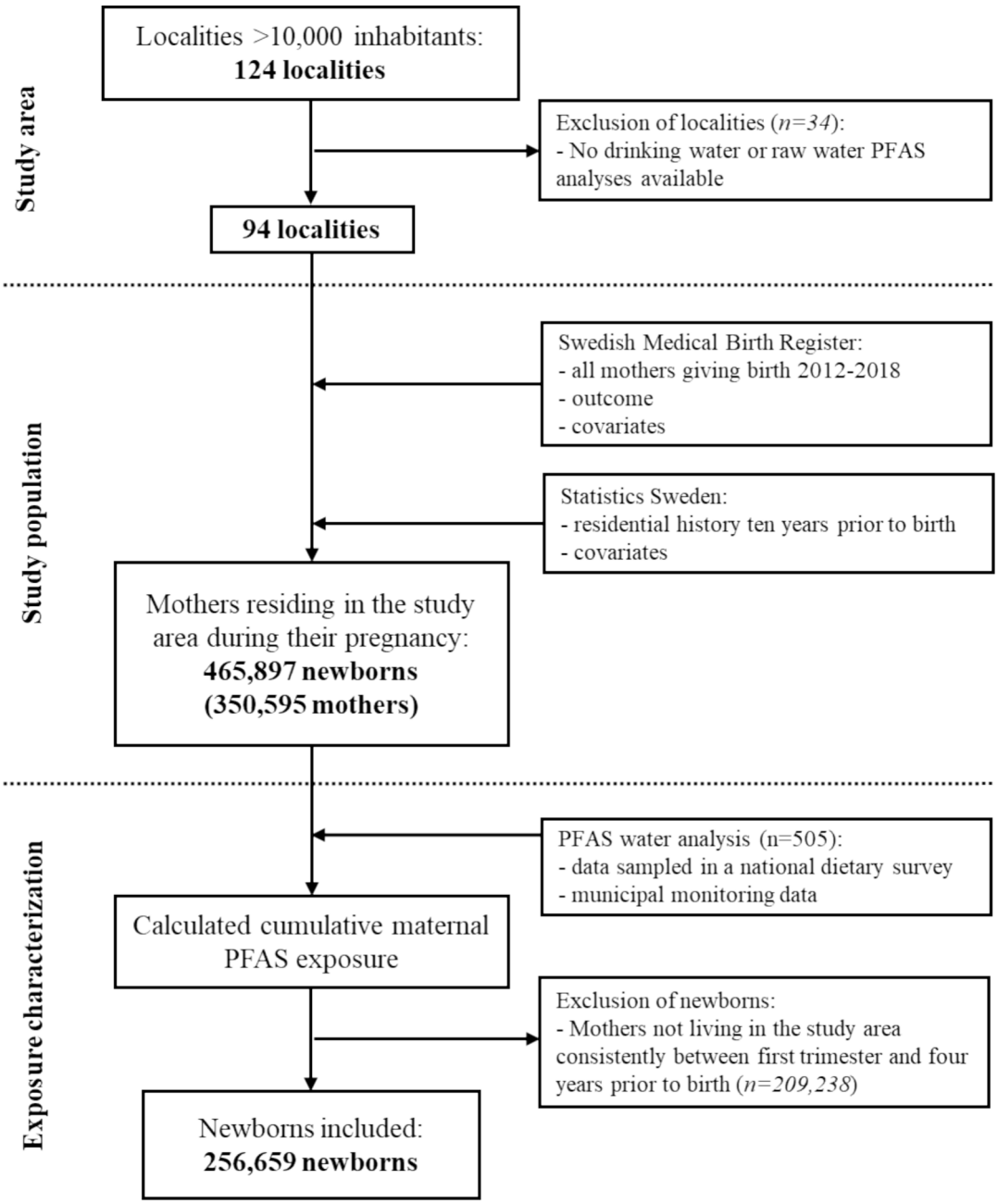



**Fig. 1.** Flow chart.

and anion exchange, that are primarily used in smaller water treatment systems. Measurements reported as either <LOQ or <LOD were treated as zero as improved analytical methods for PFAS have resulted in lower LOD/LOQ over time.

We used a one-compartment toxicokinetic model to translate the drinking water exposure to the cumulative blood PFAS concentrations of the mother at the time of each pregnancy (Eq. (1) (Bartell 2017)). The model considered the elimination rate constant of each PFAS, as well as background PFAS exposure (Miaz et al. 2020; Shu et al. 2019) and the yearly maternal drinking water exposure up to ten years before birth.

$$C_t = C_\infty + (C_0 - C_\infty) \times e^{-k*t}, \quad (1)$$

where $C_t$ is the blood PFAS concentration (ng/mL) at time ($t$) at each individual pregnancy, $C_\infty$ is the blood PFAS at steady state (ng/mL, from Eq. (2), $C_0$ is the cumulative maternal blood PFAS concentration generated from previous years, based on the exposure up to ten years prior to birth [ng/mL, the first year starting with a year-specific maternal background blood PFAS concentration (PFOS and PFNA collected in 2002–2017 (Miaz et al. 2020), and PFOA and PFHxS collected in 2007–2010 (Shu et al. 2019))], and $k$ is the elimination rate constant determined as $\frac{\ln(2)}{T1/2}$, 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 years, PFOA: 2.4 years, PFHxS: 4.5 years; females 20–55 years of age (Yu et al. 2021): PFNA: 3.4 years).

To estimate the maternal blood PFAS concentration from drinking water exposure at steady state, we applied Eq. (2) (Johanson et al. 2023).

$$C_\infty = B + C_W \times \mathrm{SWR}, \quad (2)$$

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, up to 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 individual cumulative maternal blood levels ($C_t$) were calculated separately for each PFAS.

Fetal PFAS exposure was estimated from the cumulative maternal blood PFAS concentration by using transplacental transfer efficiency (TTE) factors reported for each of the four PFAS (PFOS: 0.39, PFOA: 0.82, PFNA: 0.59, PFHxS: 0.62) from a *meta*-study (Appel et al. 2022). Hereby, we multiplied the TTE with estimated maternal PFAS blood concentration. After accounting for TTE factors, we calculated PFAS4 and categorized the modelled fetal blood PFAS4 exposure into quartiles of the exposure distribution.

### 2.3. Outcomes and covariates

From the Swedish Medical Birth Register we obtained information on congenital malformations (International Statistical Classification of Diseases and Related Health Problems 10th Revision, IDC10: Q00-Q99) diagnosed within the first 28 days *postpartum*. Congenital malformations were classified by organ system as major malformations according to the European Surveillance of Congenital Anomalies (EUROCAT 2014). Major malformations of the ear, face and neck, eye, respiratory, and abdominal wall were not included as outcome, due to limited number of cases (Table S2).

Covariates were obtained from the Swedish Medical Birth Register including maternal age, body mass index (BMI) as registered at antenatal care and smoking habits (Mattsson et al. 2015), parity and self-reported use of teratogenic drugs (class 3) (Nörby et al. 2013). Additional data on maternal country of birth, household income and highest attained maternal education were obtained from the LISA register.

### 2.4. Statistical analyses

Univariate correlations between all pairs of the four modelled fetal blood PFAS exposures were assessed using Spearman rank correlation (rho). We used logistic regression to estimate odds ratios (OR) and 95 % confidence intervals (CI) of quartiles of modelled fetal blood exposure of individual PFAS and PFAS4 and the risk of major congenital malformations. Intragroup correlation by mother was used in the regression analysis. The median modelled fetal blood concentrations within each quartile of PFAS4 exposure was used to assess the linear trend. Based on prior knowledge of potential risk factors for various congenital malformations and determinants of blood PFAS concentrations, we included in the multivariable-adjusted model the following covariates: 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$^2$), parity (nulliparа/multiparous), 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) and household income (yearly quartiles by year of birth). In the analysis of individual PFAS, each of the four PFAS were adjusted for in the model.

In addition to the main analyses, we performed a sensitivity analysis focusing on *primigravida*. As maternal blood PFAS levels are expected to be reduced as a result of parity and breastfeeding (Berg et al. 2014; Brantsaeter et al. 2013), the PFAS levels are expected to be highest among *primigravida*. We also conducted complementary analyses in which we assessed the estimated individual fetal blood PFAS exposure in mutually-adjusted multivariable logistic regression models, as well as the PFAS "mixture effect" by using quantile g-computation regression using the qgcomp package (version 2.8.6) (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

Among the 256,659 newborns included in the study, we estimated the average cumulative fetal PFAS4 exposure to 4.2 (SD: 1.4, interquartile range [IQR]: 3.7–4.3) ng/mL in blood. The distribution of all the estimated PFAS4 in the newborn is shown in Fig. S1. Of the 94 localities, 21 reported PFAS levels below LOD/LOQ, while the other had a mean PFAS4 between 0.08 and 53 ng/L (Table S1). In total, 5,357 (21 cases/1,000 births) were diagnosed with congenital malformations (Table S2). The highest prevalence of malformations was seen for congenital heart defects (4 cases/1,000 births) followed by urinary and genital defects (both 3 cases/1,000 births).

We observed minor differences in baseline characteristics across the PFAS4 exposure quartiles. Notably, the lowest PFAS quartile had the lowest household income, with incomes increasing with exposure quartiles (Table 1). The estimated individual fetal blood levels of PFOS-PFNA (rho: 0.77) and PFOA-PFHxS (rho: 0.89) were most strongly correlated (Table S3).

In the multivariable-adjusted model, when comparing the highest quartile of the modelled fetal PFAS4 exposure with the lowest quartile, we found significant associations and p-trends with malformations on the nervous system OR, 2.84 (95 % CI: 1.38–5.84, p-trend: 0.008, Table 2) and chromosomal anomalies OR, 1.50 (95 % CI: 1.07–2.20, p-trend: 0.009). For malformations of the oro-facial clefts and urinary system, we observed associations with significantly increased risk in the third but not the fourth quartile of drinking water PFAS4, compared to the lowest quartile. No corresponding associations were observed for malformations of the heart, digestive system, genitals and limbs. When restricting the analyses to *primigravida* – with approximately half the number of cases – the above indicated associations remained, although attenuated and mainly non-significant (Table S4).

We then modelled the individual PFAS fetal exposure to gain further insight into the indicated association for PFAS4 (Table S5. The associations observed for PFAS4 and malformations of nervous system and chromosomal anomalies, were in a multivariable and mutually adjusted model, including all the four single PFAS, clearly attenuated – remined non-significantly elevated for PFNA and the nervous system and for PFOS and chromosomal anomalies. However, for malformations of the urinary system, both PFOA and PFHxS were significantly associated ORs, 1.65 (95 % CI: 1.20–2.25) and 1.53 (95 % CI: 1.13–2.07), respectively, comparing extreme quartiles (Table S5). In addition, PFNA was associated with malformations of the limb, while an inverse association was observed for PFOA.

When looking deeper into the mixture and joint effects of the four PFAS, using the multivariable adjusted quantile-based g-computation models (Fig. 2), these associations were basically confirmed. A significant positive association for malformations of the urinary system (mainly driven by PFOA and PFHxS), corresponding to OR per quartile increment in the mixture of the four PFAS of 1.96 (95 % CI: 1.59–2.43, p-value: <0.001). An inverse association were seen for limbs defects (mainly driven by PFOA and PFOS).

## 4. Discussion

In this nation-wide register-based cohort, comprising more than 250,000 newborns in areas supplied by municipal drinking water in Sweden, we assessed the estimated fetal blood PFAS4 exposure in relation to congenital malformations. We observed associations between PFAS4 and corresponding increased risk of malformations of the nervous system and chromosomal anomalies. The individual PFAS analyses indicated associations primarily for PFOA and PFHxS and the urinary system, based on the model designed to assess mixture effects, resulting in 96 % increased odds per quartile increment in the mixture.

**Table 1**
Baseline population characteristics expressed as proportions of all included newborns (%) by quartiles of the modelled fetal blood exposure 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 |
|---|---|---|---|---|---|
| Estimates fetal PFAS4 ng/ml | mean (min–max) | 3.6 (3.5–3.7) | 3.9 (3.7–4.0) | 4.2 (4.0–4.3) | 5.0 (4.3–25) |
| Births included | n | 65,363 | 62,965 | 64,254 | 63,792 |
| Child characteristics | | | | | |
| Gender (%) | girl | 49 | 49 | 48 | 49 |
| | boy | 51 | 51 | 52 | 51 |
| Maternal characteristics | | | | | |
| Age (%) | <25 years | 7 | 9 | 10 | 10 |
| | 25-<30 years | 28 | 29 | 26 | 26 |
| | 30-<35 years | 37 | 37 | 37 | 37 |
| | 35-<40 years | 22 | 20 | 21 | 22 |
| | ≥40 years | 6 | 5 | 6 | 6 |
| 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 | 13 | 12 | 11 |
| | Missing | 5 | 4 | 4 | 5 |
| Parity (%) | Nulliparous | 56 | 58 | 58 | 58 |
| | Multipara | 44 | 42 | 42 | 42 |
| Smoking* (%) | No smoking | 89 | 91 | 92 | 92 |
| | 1–9 cig./day | 3 | 4 | 4 | 4 |
| | >9 cig./day | 1 | 1 | 1 | 1 |
| | Missing | 7 | 4 | 3 | 3 |
| Birth region (%) | Nordic | 74 | 71 | 70 | 71 |
| | Europe | 8 | 8 | 8 | 7 |
| | Africa | 5 | 6 | 6 | 6 |
| | North and South America | 2 | 2 | 2 | 2 |
| | Asia | 11 | 13 | 13 | 13 |
| | other | <1 | <1 | <1 | <1 |
| | Missing | 1 | 1 | 2 | 1 |
| Use of teratogenic drugs* (%) | Yes | 2 | 2 | 2 | 1 |
| | No | 98 | 98 | 98 | 99 |
| Highest attained educational level (%) | elementary school | 9 | 10 | 11 | 11 |
| | secondary education | 31 | 32 | 31 | 31 |
| | post-secondary education or higher | 59 | 56 | 57 | 56 |
| | Missing | 1 | 1 | 2 | 2 |
| Household income (quartiles by year of birth) (%) | 1st quartile | 23 | 19 | 15 | 12 |
| | 2nd quartile | 30 | 29 | 24 | 17 |
| | 3rd quartile | 24 | 28 | 31 | 33 |
| | 4th quartile | 25 | 25 | 30 | 39 |

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

The evidence of an association between PFAS and congenital malformations from experimental animal studies is sparse (DeWitt 2015) and teratogenic effects have generally not been seen in rat and mice studies (Case et al. 2001; Lau et al. 2006). If observed, this has only been at the highest exposure levels (Era et al. 2009; Thibodeaux et al. 2003), and mainly as cleft palate and congenital heart defects (Knutsen et al. 2018). Still, PFAS have been indicated to disrupt the thyroid homeostasis, which may affect the migration of the neural crest cells ultimately resulting in malformations of several organs (Bronchain et al. 2017). The clinical relevance of the findings seen in animal studies on human fetal organ development however remains unclear (Coperchini et al. 2021).

As mentioned, most epidemiological studies have reported no statistically significant associations for birth defects (Nolan et al. 2010; Savitz et al. 2012; Stein et al. 2009; Stein et al. 2014). Although these studies show good exposure contrast in PFAS blood levels, often with higher PFAS levels as compared to the estimated levels in the present study especially in the highest exposure categories, previous studies also suffer from limited power (small sample size and rare outcomes). However, there is some support of an association with craniofacial (Luo et al. 2022), brain (Stein et al. 2014) and heart defects (Ou et al. 2021). The study by Stein et al. (2014), which was part of the C8 Health Project cohort and comprised 10,000 births, reported indications of an association between PFOA and brain defects. Still, it should be mentioned that these findings were based on only thirteen self-reported cases of brain defects. In the Danish cohort study by Lou et al. (2022), comprising 656 newborns, there were indications of an association between perfluorodecanoic acid (PFDA) and craniofacial development, especially shorter palpebral fissure length (Luo et al. 2022). As craniofacial and brain tissue originate partly from the same cells (Moore et al. 2016), these tissues are likely sensitive to the same teratogens (Cerrizuela et al. 2020). PFAS have, however, been indicated to cause developmental neurotoxicity (Gaballah et al. 2020; Slotkin et al. 2008), but evidence of neurobehavioral effects in humans are inconclusive (Yao et al. 2023). In addition, the indicated association for PFAS and urinary and limb defects as well as chromosomal anomalies have not been seen in previous studies and further research is warranted, before any conclusion could be drawn on the association between PFAS and these outcomes.

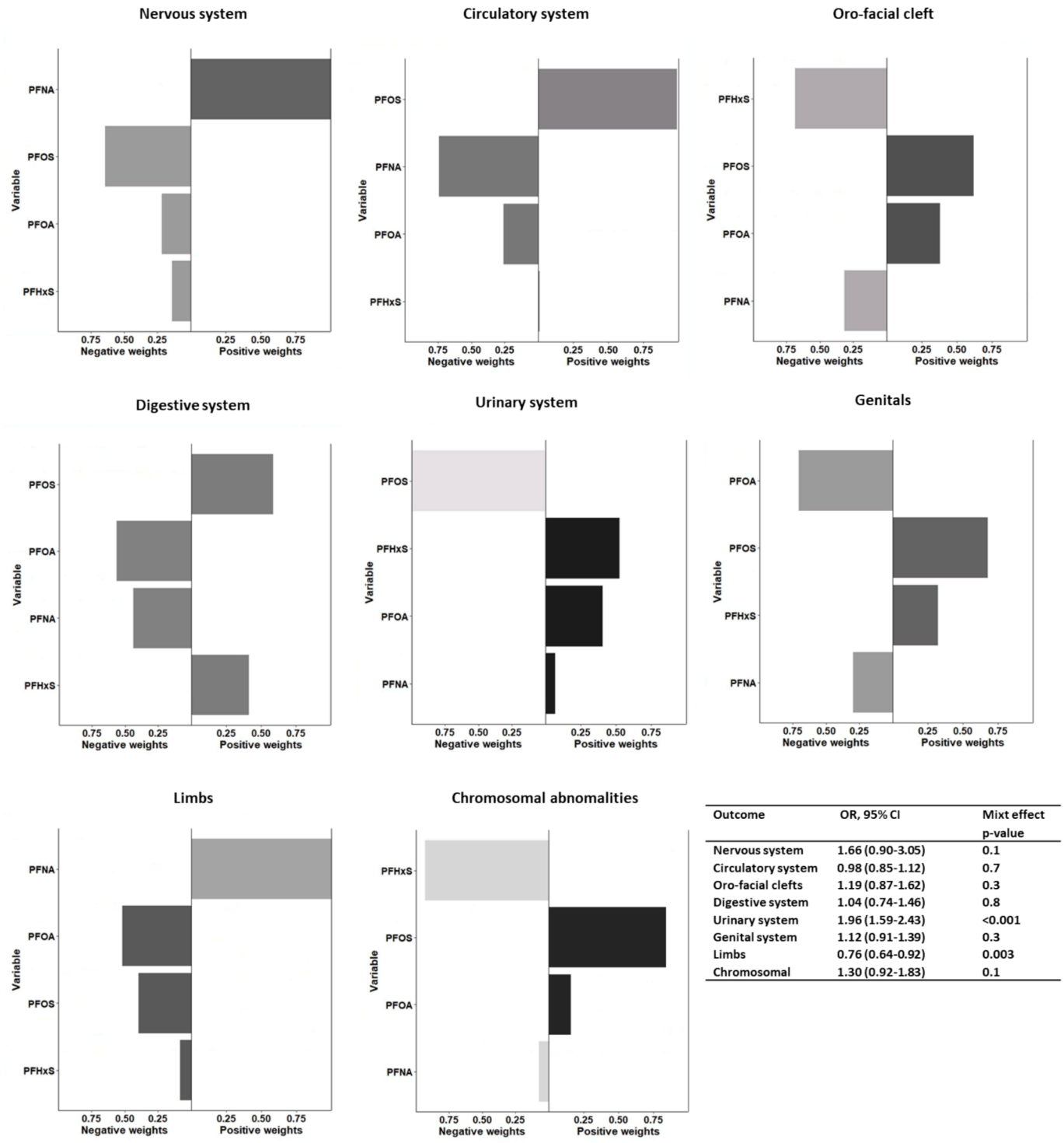
The most relevant limitation in the present study is linked to the ecological exposure assessment – resulting in a lack of individual data on drinking water consumption and on PFAS exposure from other exposure sources than the drinking water. Although we have accounted for the year-specific PFAS background blood concentrations from non-exposed pregnant women in the toxicokinetic model, to take care of the well-established PFAS exposure variation over time, the absence of information on PFAS form other sources than drinking water in the study population will introduce exposure misclassification. While using a toxicokinetic model increases the possibility to more accurately assess the internal exposure, as recently observed (Lynch et al. 2023), it is still a generic model based on one-compartment and not specific to pregnant populations. Thus, we cannot exclude that both potential inter- and intra-variability in e.g. steady-state levels, placental PFAS transfer, and other pregnancy-related events affect the PFAS-toxicokinetic which also introduce uncertainty. In addition, maternal background blood PFAS concentration may introduce some error, especially as the data originate from only two studies. Also, due to high maternal PFAS background levels, most of the drinking water PFAS levels, with exception of the highly exposed, is expected to have a limited impact on the total maternal PFAS level. This relative source contribution of drinking water was assumed to be 20 % here; thus, we recognize that to the degree that some individuals may have smaller or larger contribution from drinking water this could add some uncertainty to the estimates. Additional information of PFAS drinking water concentration and balanced sampling strategies would have been preferable to improve knowledge on potential seasonal variability and temper any potential impacts of seasonal peaks that may not be well characterized here. Although they may be some differences in seasonal variation between surface and ground

**Table 2**
Associations between the modelled fetal blood PFAS4 exposure (perfluorooctane sulfonic acid [PFOS], perfluorooctanoic acid [PFOA], perfluorononanoic acid [PFNA] and perfluorohexane sulfonic acid [PFHxS]) and major congenital malformations as diagnosed ≤28 days of life, expressed as odds ratios (OR) and 95 % confidence interval (CI) using the lowest quartile of PFAS4 exposure as reference. The study included a total of 256,659 newborns born during 2012–2018 to mothers living in large urban areas (>10,000 inhabitants) in Sweden.

| Groups of congenital malformations | Categories | Q1<br>OR | Q2<br>OR (95 % CI) | Q3<br>OR (95 % CI) | Q4<br>OR (95 % CI) | p-trend |
|---|---|---|---|---|---|---|
| Nervous system | Cases (n) | 11 | 24 | 33 | 30 | |
| | Non-cases (n) | 65,413 | 63,002 | 64,294 | 63,852 | |
| | Crude | 1.00 (ref) | **2.27 (1.11–4.62)** | **3.05 (1.54–6.04)** | **2.79 (1.40–5.58)** | |
| | Multivariable-adjusted | 1.00 (ref) | **2.23 (1.08–4.63)** | **3.03 (1.52–6.06)** | **2.84 (1.38–5.84)** | 0.008 |
| Heart Defects | Cases (n) | 489 | 451 | 493 | 453 | |
| | Non-cases (n) | 64,935 | 62,575 | 63,834 | 63,429 | |
| | Crude | 1.00 (ref) | 0.96 (0.84–1.09) | 1.03 (0.90–1.16) | 0.95 (0.83–1.08) | |
| | Multivariable-adjusted | 1.00 (ref) | 0.98 (0.86–1.12) | 1.05 (0.93–1.20) | 0.97 (0.85–1.11) | 0.7 |
| Oro-facial clefts | Cases (n) | 71 | 104 | 96 | 88 | |
| | Non-cases (n) | 65,353 | 62,922 | 64,231 | 63,794 | |
| | Crude | 1.00 (ref) | **1.52 (1.13–2.05)** | **1.38 (1.01–1.88)** | 1.27 (0.93–1.73) | |
| | Multivariable-adjusted | 1.00 (ref) | **1.52 (1.13–2.06)** | **1.38 (1.01–1.89)** | 1.30 (0.95–1.80) | 0.4 |
| Digestive system | Cases (n) | 80 | 82 | 73 | 69 | |
| | Non-cases (n) | 65,344 | 62,944 | 64,254 | 63,813 | |
| | Crude | 1.00 (ref) | 1.06 (0.78–1.45) | 0.93 (0.68–1.27) | 0.88 (0.64–1.22) | |
| | Multivariable-adjusted | 1.00 (ref) | 1.16 (0.84–1.58) | 1.02 (0.74–1.42) | 1.00 (0.71–1.39) | 0.7 |
| Urinary | Cases (n) | 164 | 220 | 234 | 182 | |
| | Non-cases (n) | 65,260 | 62,806 | 64,093 | 63,700 | |
| | Crude | 1.00 (ref) | 1.39 (1.14–1.71) | **1.45 (1.19–1.77)** | 1.14 (0.92–1.41) | |
| | Multivariable-adjusted | 1.00 (ref) | 1.39 (1.13–1.71) | **1.43 (1.17–1.74)** | 1.10 (0.88–1.37) | 0.8 |
| Genital | Cases (n) | 192 | 174 | 231 | 173 | |
| | Non-cases (n) | 65,232 | 62,852 | 64,096 | 63,709 | |
| | Crude | 1.00 (ref) | 0.94 (0.76–1.16) | 1.22 (1.01–1.49) | 0.92 (0.75–1.14) | |
| | Multivariable-adjusted | 1.00 (ref) | 0.95 (0.77–1.17) | 1.25 (1.03–1.52) | 0.94 (0.76–1.16) | 0.6 |
| Limbs | Cases (n) | 285 | 275 | 284 | 264 | |
| | Non-cases (n) | 65,139 | 62,751 | 64,043 | 63,618 | |
| | Crude | 1.00 (ref) | 1.00 (0.85–1.18) | 1.01 (0.86–1.20) | 0.95 (0.80–1.12) | |
| | Multivariable-adjusted | 1.00 (ref) | 0.99 (0.84–1.17) | 0.99 (0.84–1.17) | 0.91 (0.76–1.08) | 0.2 |
| Chromosomal | Cases (n) | 61 | 61 | 73 | 90 | |
| | Non-cases (n) | 65,363 | 62,965 | 64,254 | 63,792 | |
| | Crude | 1.00 (ref) | 1.04 (0.73–1.48) | 1.22 (0.87–1.71) | **1.51 (1.09–2.10)** | |
| | Multivariable-adjusted | 1.00 (ref) | 1.04 (0.73–1.48) | 1.21 (0.86–1.71) | **1.50 (1.07–2.11)** | 0.008 |

Models multivariable-adjusted for the following factors: maternal age, BMI (body mass index), parity, highest attained education, household income, any use of teratogenic drugs, smoking at registration to the antenatal care and country of birth.

water examined here, these patterns in Sweden are not well characterized and are also not suspected to be a major source of exposure misclassification or confounding. Therefore, we did not adjust for season as a potential confounder in our regression models. Instead, we focused on minimizing the potential effect of variations in PFAS exposure over larger time periods that may impact exposure misclassification. This effort included accounting for long-term migratory patterns when linking the drinking water PFAS concentrations to each individual, and accounting for any changes in the drinking water treatment by the water works that may have occurred. The authors also had limited data to examine long-term PFAS variability in drinking water. Thus, we acknowledge that given the mismatch between available drinking water exposure data (2014–2020) and exposure windows estimated (back to 2002), some exposure misclassification from limited measures over time is likely. Overall, we feel that the limited and unbalanced sampling data from 2014 to 2020 (sampling frequency range was from 1 to 52 with a median of 5 samples over the study period) are fairly representative of the overall trends and cumulative values over longer time-periods (including those extrapolated back to 2002 exposure windows) and should likely preserve the relative rankings of the larger exposure contrasts. The necessary exclusive use of raw water data for some of the included water works, add to a potential exposure misclassification, especially as raw water samples may in some cases overestimate the exposure in the drinking water. While additional information of PFAS drinking water concentration would have been preferable to also improve knowledge on potential seasonal variability, we focused on minimizing the potential effect of variations in PFAS exposure over time. This effort included accounting for long-term migratory patterns when linking the drinking water PFAS concentrations to each individual, and accounting for any changes in the drinking water treatment by the water works that may have occurred. In addition to this, we only included participants that received municipal drinking water (excluding rural areas potentially served by private wells). In this context it should also be mentioned that adult Swedes have a general low consumption of bottled water, while the nearly all participants reported to be consumers of at least some cold tap water (99.8 %, based on monthly 24 h estimates during a year) (Säve-Söderbergh et al. 2018). Still, the fact that we did not consider potential bottled water consumption or point source filtrations (that can remove some PFAS) into the model is a limitation, yet, sales statistics support a high consumption of tap water, as Sweden had




| Outcome | OR, 95% CI | Mixt effect p-value |
|---|---|---|
| Nervous system | 1.66 (0.90-3.05) | 0.1 |
| Circulatory system | 0.98 (0.85-1.12) | 0.7 |
| Oro-facial clefts | 1.19 (0.87-1.62) | 0.3 |
| Digestive system | 1.04 (0.74-1.46) | 0.8 |
| Urinary system | 1.96 (1.59-2.43) | <0.001 |
| Genital system | 1.12 (0.91-1.39) | 0.3 |
| Limbs | 0.76 (0.64-0.92) | 0.003 |
| Chromosomal | 1.30 (0.92-1.83) | 0.1 |

**Fig. 2.** Multivariable adjusted quantile g-computation models. The weights represent the proportion of the positive or negative partial effect for each quartile increase of modelled fetal blood exposure of PFAS4 (perfluorooctane sulfonic acid [PFOS], perfluorooctanoic acid [PFOA], perfluorononanoic acid [PFNA] and perfluorohexane sulfonic acid [PFHxS]) on the odds ratio (OR) and 95% confidence interval (CI) of major congenital malformations. Note that the length of the bars only corresponds to the relative weights of PFASs in the same direction. The darkness of the bars corresponds to the overall impact of individual PFAS on the mixture effect, which allows to make informal comparison across the left and right sides, where a large, darker bar indicates a larger independent effect than a large lighter shaded bar. The bars are darker for those malformations with the overall mixture effect is positive. Models multivariable-adjusted for the following factors: maternal age, BMI (body mass index), highest attained education, household income, any maternal use of teratogenic drugs, smoking at registration to the antenatal care and maternal country of birth.

the lowest estimated bottled water consumption per capita out of 25 EU-countries in 2019 (10 L per year, compared with 118 L per year for the EU as a whole) (Conway 2020). Thus, we put great effort into as accurately as possible rank the participants' PFAS exposure into quartiles and we observed a clear exposure contrast when comparing extreme quartiles. All this considered, the ecological exposure and assumptions linked to aggregated data usage and data availability and the lack of information on PFAS exposure from other sources than the drinking water is still a limitation that one should be aware of when interpreting the findings. Expanding the exposure information in future research has the potential to decrease the above-mentioned exposure misclassification, such as assessing individual-level exposures linked to more critical windows known for birth defects. Limitations considered; it is important to emphasize that our aim was to assess potential associations between PFAS and congenital malformation in an exploratory approach, emphasising that further research is needed, especially on underlying causal relationships. Another limitation that should be highlighted is linked to the outcome assessment. To begin with, the categorization of malformations as major malformation may potentially mask associations. The present study design and the low prevalence of malformations, only allow outcome to be aggregated into major malformation in the analysis. Another limitation is that only cases diagnosed within 28 days after birth were included. National inpatient and outpatient care register also holds data on congenital malformations, but we did not use this register to ascertain cases of congenital malformations, as it, in contrast to the Swedish Medical Birth Register, lacks a proper validation of malformations. Most severe cases are being diagnosed during the newborn period, thus assuring a high specificity in our study. Some less severe malformations are likely to be underdiagnosed, like certain heart defects, which should be considered when interpretating the findings. In addition, the use of major malformations instead of minor, may result in lack in sensitivity and the lack of identifying an association linked to differences in the etiology. In addition, there is a risk of introducing a live birth bias, as we did not have information on potential malformation among induced or spontaneous abortions. This is however impossible to fully consider, as malformation are not assessed in most of these cases. Still, the overall prevalence of major congenital malformation in the present study agrees well with the reported national prevalence (21 cases/1,000 births, excluding terminated pregnancies) 2007–2015 (EUROCAT 2020).

Despite shortcomings, given the low prevalence of congenital malformation, studies assessing the association between PFAS and congenital malformations requires a large study population to gain sufficient statistical power. A register-based study design and an ecological exposure assessment was therefore considered appropriate, especially as teratogenicity of PFAS is not yet well studied. Moreover, by using the nation-wide register-based approach, we have generated one of the largest studies ever on this topic by including more than 250,000 newborns. We were also able to adjust for most relevant covariates at an individual level, and had access to socio-economic information, long-term residential information as well as medically confirmed diagnosis of malformation via administrative and medical records. Moreover, we had also information on maternal smoking habits during gestation, which has previously been validated using cotinine (Mattsson et al. 2015). Due to decades of publicly funded antenatal and delivery care and mandatory collection of data in administrative register, these register have a high coverage, close to 100 % of all completed pregnancies in Sweden (Källén and Källén 2003; Ludvigsson et al. 2016), avoiding any selection linked to recruitment. Finally, while it is likely that we were able to adjust for most relevant confounders, there are some exceptions, like differences in the use of folic acid supplements. Folic acid is well known to reduce the risk of malformations in situations with insufficient intake, but have also been indicated to inversely linked to PFAS levels (Tian et al. 2022). While food is not fortified with folic acid in Sweden, women planning a pregnancy within a few months are advised by authorities to take folic acid supplements up to gestational week 12 (Czeizel et al. 2013). The supplement use is expected to be highly underreported in the Swedish Medical Birth Register (NBHW 2018), and was therefore not considered reliable enough to be included in our models. However, there are indications that socioeconomic factors may affect the use (Murto et al. 2017), and as an indirect surrogate for the use of folic acid supplements we adjusted for several socioeconomic-related factors (highest attained educational level, household income and maternal birth country). Still, there is a risk that residual confounding remains a concern for folic acid and some other covariates, especially for outcomes like neural tube defects. To clarify this important issue, future studies should inquire if folate affects the toxicokinetic of PFAS and prospective cohort studies should try to gather high quality self-reports on folic acid supplement use.

In conclusion, in the present study there are indications that modelled fetal blood PFAS4 exposure were significantly associated with malformation of nervous system and chromosomal anomalies. The individual PFAS analyses indicated that PFOA and PFHxS were associated with increased risk of malformation of the urinary system, also driving the overall mixture effect. Yet, contrasting association were observed for defects on the limbs. As the underlying toxicological mechanisms remains unclear and the evidence from both animal and human studies is limited, the indicated associations in the present study should be interpreted with caution, as chance findings may not be excluded. Still, further research is needed to explore the indicated association with malformations of the nervous system, urinary system, limb and the chromosomal anomalies more in detail.

## CRediT authorship contribution statement

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

## 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.2025.109381.

## Data availability

The data that has been used is confidential.

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