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Per- and polyfluoroalkyl substances (PFAS) in drinking water, gestational diabetes mellitus, hypertension and preeclampsia: A nation-wide register-based study on PFAS in drinking water

Melle Säve-Söderbergh [a,b,1,*], Irina Gyllenhammar [a,c], Tessa Schillemans [b], Emelie Lindfeldt [a], Carolina Vogs [c], Carolina Donat-Vargas [b,d], Emilie Helte [b], Emma Ankarberg [a], Anders Glynn [c], Lutz Ahrens [e], Agneta Åkesson [b]

[a] Science Division, Swedish Food Agency, Uppsala, Sweden
[b] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[c] Department of Animal Biosciences, Swedish University of Agricultural Sciences (SLU), Uppsala, Sweden
[d] Barcelona Intitute for Global Health (ISGlobal), Barcelona, Spain
[e] Department of Aquatic Sciences and Assessment, Swedish University of Agricultural Sciences (SLU), Uppsala, Sweden

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ABSTRACT

Background: There is inconclusive evidence of associations between exposure to per- and polyfluoroalkyl substances (PFAS) and diabetes and hypertensive disorders during pregnancy.
Objectives: We conducted a nation-wide register-based cohort study to assess the associations of the estimated maternal drinking water exposure to the sum of four major PFAS (PFAS4; perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorononanoate (PFNA) and perfluorohexanoate (PFHxS)) with gestational diabetes mellitus (GDM), hypertension and preeclampsia.
Materials and methods: We included nulliparous women giving birth in Sweden during 2012–2018 in large 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 considering residential history, municipal PFAS water concentration and year-specific maternal PFAS background serum levels. The outcomes and individual covariates were ascertained via register linkage. Mean values and 95% Confidence Intervals (CI) of Odds Ratios (OR) were estimated by logistic regression.
Results: Among the 109,031 nulliparous women included, with an estimated average 7.8 ng PFAS4/mL serum (standard deviation: 2.0 ng/mL), there were indications of a non-monotonic inverse association for PFAS4 and GDM, corresponding to multivariable-adjusted OR 0.72 (95 % CI: 0.61–0.84) when comparing extreme quartiles. An inverse association were also seen for each PFAS individually. No clear associations were seen for hypertension or preeclampsia, although individual PFAS indicated significant associations, both inverse (PFAS and PFHxS) and direct (PFOS and PFNA) for hypertension.
Conclusion: In the present study, we observed indications of inverse, non-monotonic associations for PFAS4 and GDM. Some individual PFAS were also associated with hypertension, both direct and inverse. The limitations linked to the exposure assessment still require caution in the interpretation.

1. Introduction

The most common health complications during pregnancy are metabolic disorders, like Gestational Diabetes Mellitus (GDM) and hypertensive disorder. GDM affects 14 % of all pregnant women globally, with large regional differences in the prevalence (Wang et al. 2022a). Hypertension disorder is an umbrella term of several hypertensive disorders with different stages of severity and it is estimated that around 10 % of all expectant mothers will suffer from some type of hypertension during their pregnancy (Cunningham et al. 2009). The most severe cases

* 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 adress: Institute of Environmental Medicine, Nobels väg 13, 171 65 Solna.

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of hypertension are preeclampsia and eclampsia, which occur among 4.6 % and 1.4 % of all pregnant women, respectively (Abalos et al. 2013). (Pre)eclampsia can lead to severe and sometimes fatal complications for both the mother and unborn child. These may include fetal growth restriction, preterm birth and maternal organ injury. GDM and hypertension have similarities in terms of pathophysiology and shared risk factors, like obesity, advanced maternal age and parity (Yang and Wu 2022). While several risk factors are known, there are indications that environmental contaminants may be relevant determinants of illness (Erinc et al. 2021; Yan et al. 2022).

Owing to their high chemical stability, combined with hydrophobic and oleophobic properties, per- and polyfluoroalkyl substances (PFAS) have for decades been used in a wide range of industrial processes and commercial products (Gluge et al. 2020; Houde et al. 2006). Nevertheless, these chemical attributes also make PFAS highly persistent, leading to their ubiquitous presence in both the environment and the human body (Sunderland et al. 2019). Several PFAS have indicated to disrupt placental and immune function, cause oxidative stress, and disrupt lipid metabolism (Erinc et al. 2021). During recent years, an increasing number of epidemiological studies have explored whether PFAS are a risk factor for GDM and hypertension. The most recent review and *meta*-analysis suggests that perfluorooctanoate (PFOA) and perfluorobutanesulfonate (PFBS) may be associated with GDM (Yan et al. 2022), and associations with increased risk has also been seen in more recent studies for several different PFAS, especially for PFOA (Peterson et al. 2023; Zang et al. 2023; Zhang et al. 2023). Exposure to perfluorooctane sulfonate (PFOS) has also been linked to a higher risk of preeclampsia, whereas perfluoroundecanoate (PFUnDA) has been associated with a reduced risk (Gao et al. 2021). However, in more recent studies, no clear associations have been observed for either compound (Birukov et al. 2021; Preston et al. 2022). The populations in these studies are often small, thus resulting in limited statistical power, and the exposure assessment is often based on PFAS measurements in maternal blood (serum or plasma). Concerns have been raised on the potential introduction of confounding or reverse causality due to the plasma volume expansion, as well as variations in glomerular filtration rate and albumin excretion that takes place during pregnancy (Cheung and Lafayette 2013; Verner et al. 2015).

To further explore and elucidate the potential association of PFAS exposure and the risk of GDM, hypertension and preeclampsia, we conducted a nation-wide register-based prospective cohort study among nulliparous women in Sweden that gave birth during 2012–2018. We used a retrospective locality-specific maternal exposure, in which we estimated cumulative maternal blood PFAS at the beginning of pregnancy by applying a toxicokinetic model that included the levels of PFAS in each of the pregnant women's municipal drinking water together with general year-specific background PFAS levels in pregnant women.

2. Methods

2.1. Study area and population

The study area, population and exposure assessment have previously been described (Säve-Söderbergh et al. 2024). In short, we identified all Swedish localities (coherent and densely populated urban areas) with a population of > 10,000 inhabitants in 2015 (n = 124, ~60 % of the Swedish population) to be able to correctly link all residences to their municipal drinking water works. In case more than one water work was responsible for the water supply in the locality, specific distribution areas were identified by DeSO-codes (Demographic Statistics Areas) from the Geodatabase at Statistics Sweden. Next, we excluded localities (either parts or entire localities) for which PFAS water data were not available, leaving 94 localities for inclusion (~40 % of the Swedish population) in the study. The study population included all mothers who lived in the study area at any time during pregnancy and gave birth (live or stillbirth) between January 1st 2012 to December 31st 2018 (n = 350,595 mothers). To minimize the risk of exposure misclassification, we excluded mothers who had resided outside the study area for four years or more before giving birth (excluding 146,766 mothers). Moreover, to avoid any effect of parity on PFAS elimination as well as on the risk of GDM and hypertensive disorders, we only included nulliparous mothers (excluding 94,798 mothers/births), leaving 109,031 nulliparous mothers for inclusion in the study.

Health care and administrative (income, residential history, etc.) data was obtained by linking the maternal personal identification number (a unique identification number assigned to all Swedes), to the 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). Yearly information on residential history ten years before birth was obtained from the national register for regional divisions based on real estate using the Geodatabase.

2.2. Exposure

PFAS data for raw and drinking water were obtained from a nationally representative survey, Riksmaten Adolescence, in which samples were taken in 2018 and analysed at the Swedish University of Agricultural Sciences (Nyström-Kandola et al. 2023). Data were also obtained from municipal monitoring data sampled in 2014–2020 (Lindfeldt et al. 2021), analysed primarily at commercial laboratories. Last, data was collected from personal communication with three drinking water producers in PFAS hotspot areas, on levels measured before 2014. In total, we obtained 505 water analyses (305 raw water and 200 drinking water samples).

To estimate PFAS exposure, we used the sum of four major PFAS (PFAS4; perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), perfluorononanoate (PFNA) and perfluorohexanoate (PFHxS)). Other PFAS were not considered since these were mainly < limit of detection/quantification (LOD/LOQ) and/or not measured. In addition to this, recent studies among Swedes have indicated a low bioaccumulation of these PFAS (Nyström-Kandola et al. 2023; Nyström et al. 2022). From the drinking water concentrations, we calculated one locality-specific average for each of the four PFAS during the study period. Raw water concentrations were only used when no drinking water data were available, or when the average sum of PFAS4 differed by less than 5 ng/L between raw and drinking water, or the differences in PFAS4 concentrations in raw and drinking water were non-significant ($p > 0.05$, Student's *t*-test) between raw and drinking water samples. This was done to maximize the reliability of the mean values used. Due to differences in LOQ/LOD between years, measurements of either < LOQ or < LOD were treated as zero. More details on the drinking water PFAS concentrations per locality are found in Säve-Söderbergh et al. 2024.

We then used a one-compartment toxicokinetic model (Bartell 2017) to estimate the cumulative maternal serum PFAS concentrations at the beginning of each woman's pregnancy (represented by C_0 in Equation (1). The model considers the elimination rate of each of the four PFAS, the cumulative background PFAS exposure and the yearly maternal drinking water exposure up to ten years prior to the birth (based on the information on maternal migratory patterns).

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

where C_t is the final maternal drinking water-related serum PFAS concentration at time t (ng/mL) representing the time of pregnancy for each single women, C_∞ is the drinking water-related serum PFAS at steady state (ng/mL, see Equation (2), C_0 is the initial serum PFAS concentration (ng/mL, background levels (B) during first year) and k is the elimination rate constant determined as $\frac{\ln(2)}{T1/2}$, where $T½$ is the half-life of each of the four PFAS (PFOS: 3.4 years, PFOA: 2.7 years, PFNA: 3.5 years, PFHxS: 5.3 years) (Ojo et al. 2021).

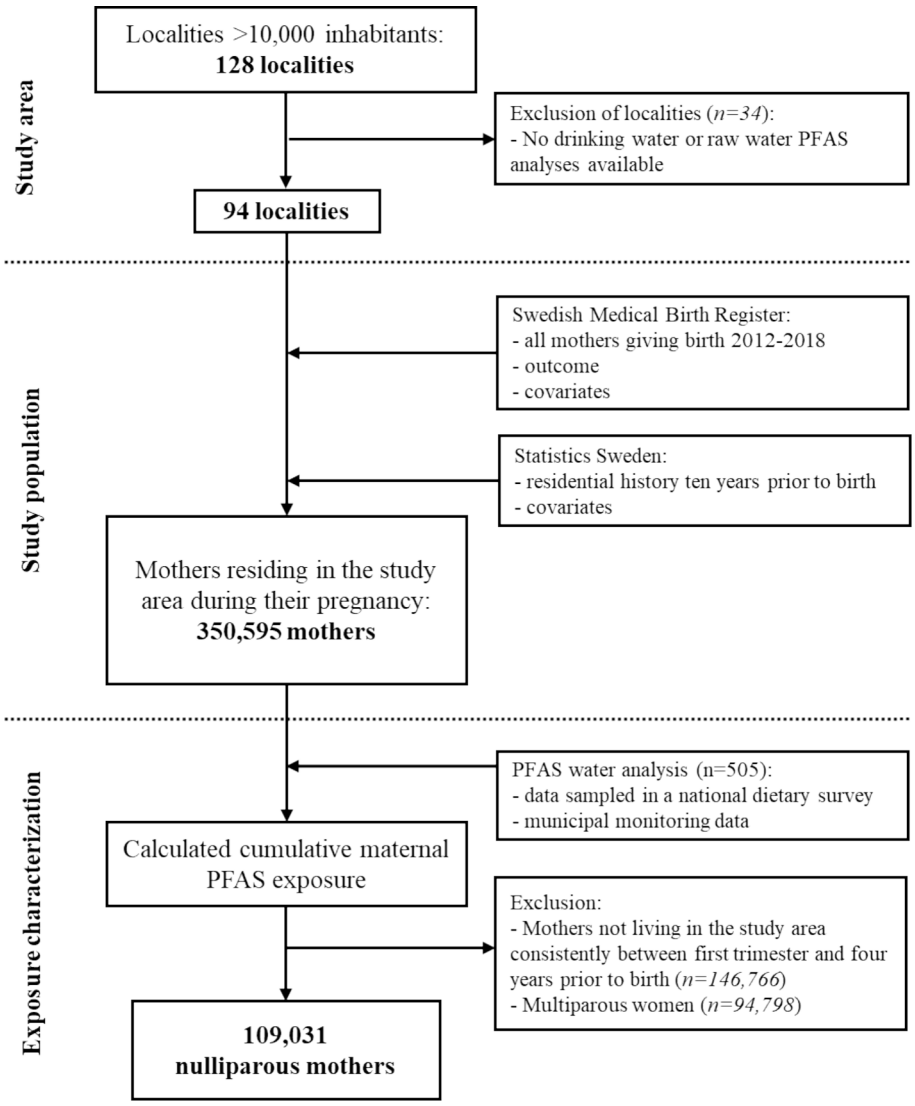

Fig. 1. Study area, study population and exposure of PFAS.

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

where B is the time-specific maternal background serum PFAS concentration for each calendar year, until ten years prior to birth (ng/mL), C_W is the locality-specific average PFAS water concentration according to maternal residency each year, ten years prior to birth (ng/L), *SWR* is the steady-state ratio of serum:water PFAS concentrations for females (Johanson et al. 2023). The yearly average maternal background PFAS serum concentrations (B) were obtained for PFOS and PFNA during the period 2002–2017 and for PFOA and PFHxS during 2007–2010 (Miaz et al. 2020; Shu et al. 2019). When data of background concentrations for a specific year was missing, we used the closest retrospective year of serum PFAS available. The cumulative maternal serum levels (C_t) were calculated separately for each PFAS and then summed to PFAS4 (Supplemental Fig. S1). Finally, the mothers were categorised into PFAS4 quartiles according to their exposure.

2.3. Outcomes and covariates

Data on GDM, gestational hypertension and preeclampsia were obtained from in- and outpatient care, stored in the Patient Register at National Board of Health and Welfare. As primary outcomes, we obtained data on GDM (International Statistical Classification of Diseases and Related Health Problems 10th Revision, ICD10: O24.4) hypertension (ICD10: 13.9 and O14) and preeclampsia (ICD10: O14). We additionally excluded cases of pregestational diabetes type I and type II (ICD10: O24:0-O24.3) when assessing the risk of GDM, and pregestational hypertension (ICD10: O10) when assessing hypertension and preeclampsia (Table S1). Information on maternal age, body mass index (BMI) and smoking habits were obtained from the Swedish Medical Birth Register, while country of birth, household income and highest attained education were obtained from Statistics Sweden.

2.4. Statistical analyses

Multivariable-adjusted logistic regression was used to assess the association of PFAS4 quartiles with GDM, hypertension and preeclampsia expressed as Odds Ratios (OR) and 95 % Confidence Intervals (CI). The median PFAS4 concentrations within each exposure category were used to assess the linear trend. Based on prior knowledge of potential risk factors for GDM, hypertension and preeclampsia and determinants of serum PFAS concentrations (Yang and Wu 2022), 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), smoking at registration to antenatal care (no smoking, 1–9 cigarettes/day, >9 cigarettes/day), mother's country of

birth (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). Missing data was treated as null for BMI (4 %) and smoking status (4 %). Adding to the multivariable-adjusted model, a factor aiming to capture any potential contextual confounding, did not affect the risk estimates and were thus not retained in any of the models.

To further explore the linear dose–response relationship we plotted the data using restricted cubic splines with three knots of the distribution (at the 10th, 50th and 90th percentiles of the distribution) (Orsini and Greenland 2011). To reduce the impact from outliers, we excluded the highest 1 % of the estimated PFAS4 levels in the spline analysis. To gain deeper insight of the individual PFAS, their associations with the outcomes were also assessed separately. 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

Of the 109,031 nulliparous mothers included in the study 1,289, 6,886 and 4,408 were diagnosed with GDM, gestational hypertension and preeclampsia, respectively. Based on the average PFAS levels in drinking water and the year-specific maternal background levels, the cumulative blood PFAS4 levels among the women were on average 7.8 ng PFAS4/mL serum (standard deviation: 2.0 ng/mL, 5th and 95th percentile: 6.4 ng/mL and 8.9 ng/mL). Across PFAS4 quartiles, we observed only small differences in maternal baseline characteristics, except for household income. In the lowest PFAS4 exposure quartile, there was a higher proportion of mothers with the lowest income and a lower proportion of mothers with the highest income, while the opposite trend was noted in the highest PFAS4 exposure quartile (Table 1).

After multivariable adjustment, PFAS4 was inversely associated with GDM, OR 0.72 (95 % CI: 0.61–0.84, p-trend: <0.001, Table 2), comparing the highest exposure quartile with the lowest. Inverse associations were also seen for individual PFAS when comparing extreme quartiles (PFOS: OR 0.76, 95 % CI: 0.64–0.89, p-trend: 0.001; PFOA: OR 0.47, 95 % CI: 0.39–0.57, p-trend: <0.001; PFNA: OR 0.81, 95 % CI: 0.69–0.95, p-trend: <0.001; PFHxS: OR 0.74, 95 % CI: 0.63–0.88, p-trend: <0.001; Table S2). In the restricted cubic spline analysis, there were indications that the inverse association flattened out at the highest exposure, suggesting a potential non-monotonic dose–response relationship (Fig. 2).

A borderline statistically significant inverse association was seen for PFAS4 and hypertension, OR 0.93 (95 % CI: 0.86–1.00, p-trend: 0.04, Table 2, Fig. 3), no significant associations were observed for preeclampsia, 1.01 (95 % CI: 0.92–1.10, p-trend: 0.8, Table 2, Fig. 4), when comparing extreme quartiles. When assessing individual PFAS, PFOS and PFNA were each inversely associated with hypertension (PFOS: OR 0.91, 95 % CI: 0.84–0.97, p-trend: 0.003; PFNA: OR 0.90, 95 % CI: 0.84–0.97, p-trend: 0.004; Table S2). In contrast, PFOA and PFHxS were directly associated with an increased risk of hypertension (PFOA: OR 1.16, 95 % CI: 1.08–1.25, p-trend: <0.001; PFHxS: OR 1.20, 95 % CI: 1.12–1.29, p-trend: <0.001; Table S2). None of the individual PFAS were associated with preeclampsia, with the exception of PFHxS which was inversely associated with preeclampsia, but without statistically significant trend (OR 0.88, 95 % CI: 0.81–0.96, p-trend: 0.1; Table S2).

4. Discussion

In this nation-wide register-based cohort, including more than 100,000 nulliparous women living in Sweden, we assessed if predicted cumulative maternal serum PFAS4 concentrations, accounting for the locality specific drinking water content, were associated with the risk of GDM, hypertension and preeclampsia. The results suggest an inverse association of PFAS4 with GDM. This inverse association remained for all the individual PFAS. Mainly no associations were seen for PFAS4 and hypertension and preeclampsia, although individual PFAS indicated significant associations with both lower (PFAS and PFHxS) and higher odds (PFOS and PFNA) of hypertension.

The most recent review and *meta*-analysis assessing PFAS and GDM, suggest an association for blood/serum levels of PFOA and PFBS with increased risk of GDM (Yan et al. 2022). Other PFAS have also been suggested to be positively associated with GDM, but results are mixed and there are large inconsistencies across studies (Liu et al. 2019; Preston et al. 2020; Rahman et al. 2019; Wang et al. 2022b; Wang et al. 2018; Xu et al. 2020; Yu et al. 2021; Zang et al. 2023; Zhang et al. 2023). In line with our findings, some studies have reported statistically significant inverse associations for some PFAS – like PFHxS – and GDM (Peterson et al. 2023; Xu et al. 2022).

For hypertensive disorders, the most recent review and *meta*-analysis indicated a direct association of PFOA with preeclampsia (pooled OR per 1-log increase: 1.27, 95 % CI: 1.06–1.51), while an inverse association was observed for PFUnDA (pooled OR per 1-log increase: 0.81, 95 % CI:

Table 1
Baseline population characteristics expressed as proportions of all included pregnant women (%) by quartiles of the cumulative maternal exposure of the sum of PFAS4 (perfluorooctane sulfonate [PFOS], perfluorooctanoate [PFOA], perfluorononanoate [PFNA] and perfluorohexane sulfonate [PFHxS]). The study included a total of 109,031 nulliparous women during 2012–2018 to mothers living in large urban areas (>10,000 inhabitants) in Sweden.

Variables	Categories	Q1	Q2	Q3	Q3
PFAS4 ng/mL	mean (min–max)	6.6 (6.4–6.8)	7.2 (6.8–7.5)	7.9 (7.5–8.3)	8.8 (8.3–396)
Mothers included	n	27,270	27,272	27,349	27,140
Age (%)	<25 years	12	15	17	16
	25-<30 years	36	37	33	33
	30-<35 years	35	33	34	34
	35-<40 years	14	12	13	13
	>40 years	3	3	4	3
Body mass index (BMI, %)[a]	<18.5	3	3	3	3
	18.5-<25	60	62	64	64
	25-<30	21	21	20	20
	≥30	10	10	9	8
Smoking (%)[a,b]	No smoking	89	92	92	92
	1–9 cigarette/day	3	3	4	4
	>9 cigarette/day	1	1	1	1
Birth region (%)	Nordic	81	78	78	78
	Europe	7	7	7	7
	Africa	3	3	3	4
	North and South America	1	2	2	2
	Asia	8	10	9	10
	other	<1	<1	<1	<1
Highest attained educational level (%)	elementary school	6	7	8	8
	secondary education	30	31	31	31
	post-secondary education or higher	64	62	61	61
Household income (quartiles by year of birth, %)	1st quartile	26	21	19	15
	2nd quartile	29	31	26	17
	3rd quartile	22	26	30	33
	4th quartile	22	22	26	35

[a] Missing data: BMI (4%) and smoking status (4%).
[b] As reported at registration to antenatal care.

Table 2
Associations between the cumulative exposure of the sum of PFAS4 (perfluorooctane sulfonate [PFOS], perfluorooctanoate [PFOA], perfluorononanoate [PFNA] and perfluorohexane sulfonate [PFHxS]) from locality-specific municipal drinking water and default background exposure and gestational diabetes mellitus (GDM), hypertensive disorders during pregnancy (HP) and preeclampsia (PE), expressed as odds ratios (OR) and 95 % confidence interval (CI) and using the lowest quartile of PFAS exposure as reference. The study included a total of 109,031 nulliparous women during 2012–2018 to mothers living in large urban areas (>10,000 inhabitants) in Sweden.[a]

		Total mothers	Q1 OR	Q2 OR (95 % CI)	Q3 OR (95 % CI)	Q4 OR (95 % CI)	p-trend
GDM	Cases (n)		417	327	276	269	
	Non-cases (n)	108,364	26,794	26,694	26,773	26,814	
	Crude		1.00 (ref)	0.79 (0.68–0.91)	0.66 (0.57–0.77)	0.64 (0.55–0.75)	
	Multivariable-adjusted		1.00 (ref)	0.79 (0.68–0.92)	0.72 (0.61–0.84)	0.72 (0.61–0.84)	<0.001
HP	Cases (n)		1,846	1,724	1,677	1,639	
	Non-cases (n)	108,280	25,337	25,275	25,363	25,419	
	Crude		1.00 (ref)	0.94 (0.87–1.00)	0.91 (0.85–0.97)	0.89 (0.83–0.95)	
	Multivariable-adjusted		1.00 (ref)	0.96 (0.90–1.03)	0.94 (0.88–1.01)	0.93 (0.86–1.00)	0.04
PE	Cases (n)		1,131	1,095	1,100	1,082	
	Non-cases (n)	108,662	26,158	26,009	26,024	26,063	
	Crude		1.00 (ref)	0.97 (0.89–1.06)	0.98 (0.90–1.06)	0.96 (0.88–1.05)	
	Multivariable-adjusted		1.00 (ref)	1.00 (0.92–1.09)	1.02 (0.93–1.11)	1.01 (0.92–1.10)	0.8

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

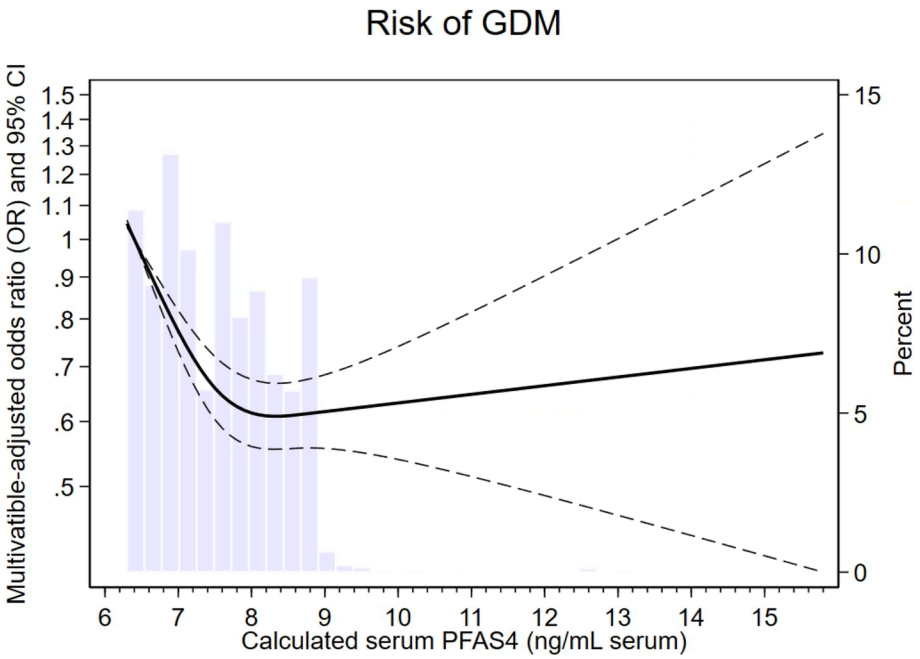

Fig. 2. Multivariable-adjusted Odds Ratios (OR) and 95 % Confidence Intervals (CI) of the first 99 % of the estimated cumulative maternal blood levels of PFAS4 (ng/mL, based on a one-compartment toxicokinetic model) (sum of perfluorooctane sulfonate [PFOS], perfluorooctanoate [PFOA], perfluorononanoate [PFNA] and perfluorohexane sulfonate [PFHxS]) and the risk Gestational Diabetes Mellitus (GDM) 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, as well as the percentage of the total population (blue bars and the right y-axis). The study included a total of 109,031 nulliparous women during 2012–2018 to mothers living in large urban areas (>10,000 inhabitants) in Sweden. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

0.71–0.93) (Gao et al. 2021). More recent studies have mainly reported similar findings (Bommarito et al. 2021; Law et al. 2023; Liu et al. 2022; Preston et al. 2022; Zhu and Bartell 2022). As for GDM, there are large inconsistencies regarding which PFAS is driving the association, and only PFOS has been directly linked to the risk of hypertensive disorders in more than one study (Bommarito et al. 2021; Liu et al. 2022; Preston et al. 2022; Wikström et al. 2019).

Of the studies using a locality-specific ecological study design for the exposure, findings are also somewhat inconsistent. In a large US study by Zhu and Bartell (2022), including more than eight million pregnancies, PFHxS was directly associated with odds of hypertension (OR 1.12; 95 % CI: 1.08–1.15), while an inverse association were seen for PFOA 0.91 (95 % CI 0.88–0.94). We also observed a direct association for PFHxS and hypertension, but no inverse association with PFOA. In an Australian cohort comprising 16,970 pregnancies from PFAS exposed and unexposed areas found a direct association for hypertensive disorder (RR: 1.88; 95 % CI: 1.30–2.73) in one of the PFAS exposed areas compared to the unexposed (Law et al. 2023). Finally, in a highly exposed Swedish area, a study comprising of 27,292 pregnancies, observed no association with an increased risk of preeclampsia in the exposed groups (Ebel et al. 2023). The authors did not estimate individual PFAS levels in that study, but individual serum PFAS levels had

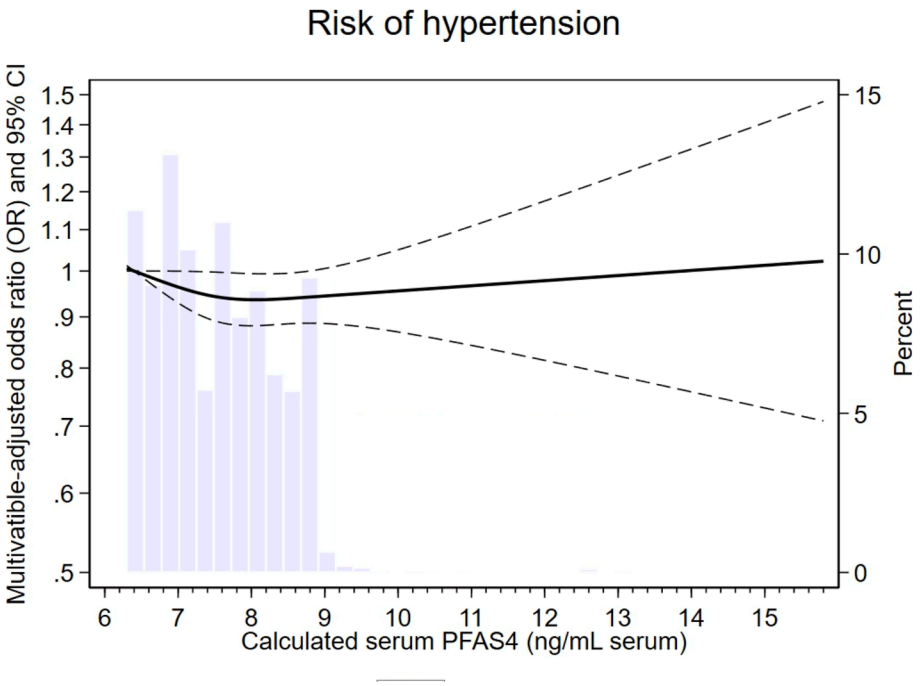

Fig. 3. Multivariable-adjusted Odds Ratios (OR) and 95 % Confidence Intervals (CI) of the first 99 % of the estimated cumulative maternal blood levels of PFAS4 (ng/mL, based on a one-compartment toxicokinetic model) (sum of perfluorooctane sulfonic acid [PFOS], perfluorooctanoic acid [PFOA], perfluorononanoic acid [PFNA] and perfluorohexane sulfonic acid [PFHxS]) and the risk hypertension during pregnancy 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, as well as the percentage of the total population (blue bars and the right y-axis). The study included a total of 109,031 nulliparous women during 2012–2018 to mothers living in large urban areas (>10,000 inhabitants) in Sweden. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

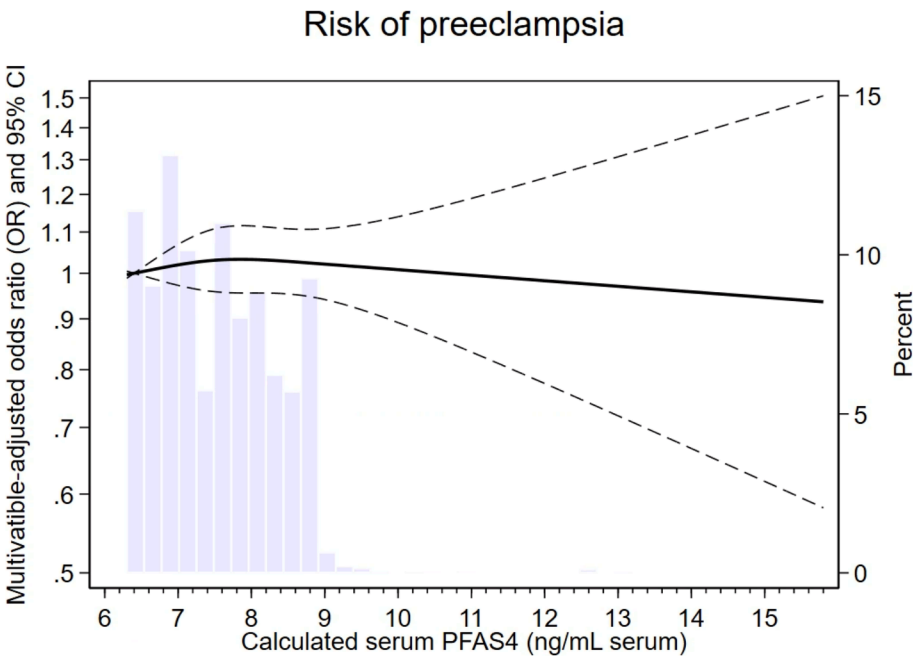

Fig. 4. Multivariable-adjusted odds ratios (OR) and 95 % confidence intervals (CI) of the first 99 % of the estimated cumulative maternal blood levels of PFAS4 (ng/mL, based on a one-compartment toxicokinetic model) (sum of perfluorooctane sulfonic acid [PFOS], perfluorooctanoic acid [PFOA], perfluorononanoic acid [PFNA] and perfluorohexane sulfonic acid [PFHxS]) and the risk preeclampsia 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, as well as the percentage of the total population (blue bars and the right y-axis). The study included a total of 109,031 nulliparous women during 2012–2018 to mothers living in large urban areas (>10,000 inhabitants) in Sweden. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

been analysed in a subset of the study population showing large differences in serum levels between the three categories: background, intermediate and high exposure.

In addition, there is increasing evidence supporting a non-monotonic association between PFAS exposure and GDM, gestational hypertension and preeclampsia (Birukov et al. 2021; Duan et al. 2021; Dunder et al. 2023; Gui et al. 2023; Liu et al. 2022; Preston et al. 2020), which also could explain some of the inconsistencies in the existing epidemiological literature, especially when exposure range differs. Interestingly, a recent study among 2,373 adult Swedes, found a non-monotonic association between PFOA and diabetes among the women in the study, indicating an inverse dose response at low PFAS levels, that turning into an association with increased risk at higher exposure levels (Dunder et al. 2023). This is in line with our results from the restricted cubic spline analysis, showing that the inverse association of PFAS4 with GDM, may change direction at higher exposure levels.

While the mechanisms behind hypertension, preeclampsia and GDM development are not fully understood, multiple aetiologies have been proposed – that potentially could influence the association in several directions. There is increasing evidence that PFAS may disturb the glucose metabolism, insulin secretion (Roth and Petriello 2022) and thyroid hormone homeostasis (Birru et al. 2021). It has been indicated that PFAS exposure may disturb the metabolic actions of insulin, through interference with the β-cell function and hepatic glycogen synthesis (Cardenas et al. 2017; Yan et al. 2015). Proposed mechanisms for hypertensive disorders include systemic inflammation and oxidative stress, predisposing cardiovascular and endothelial dysfunction (Steegers et al. 2010). On the other hand, several PFAS can activate different isoforms of the Peroxisome Proliferator-Activated Receptor (PPAR) (Almeida et al. 2021; Behr et al. 2020), which are recognized as anti-inflammatory agents (Usuda and Kanda 2014) and implicated in blood pressure regulation. PPARs also plays a critical role in lipid and glucose metabolism (Grygiel-Górniak 2014) and receptor agonists like fibrates have been used to clinically treat dyslipidemia and hypertriglyceridemia (Staels et al. 1997). Therefore, it is possible that several mechanisms may influence relations between PFAS exposure and GDM in both directions depending on the PFAS in question and the exposure levels: i.e. cause decreased risks, as observed by us, or increased risks observed in other studies. This could explain the inconsistencies between epidemiological studies, as well as the non-monotonic dose–response relationships between PFAS4 and GDM.

Some limitations in the study need to be addressed, mostly being related to the exposure estimation. Although using an ecological exposure has the benefit of being resistant to physiological confounding, the proxy of the exposure used in the present study only reflects tap water consumption as a route of PFAS exposure taking into account background PFAS concentrations in serum in Sweden in general terms. While we were able to obtain data for a large part of the largest Swedish localities, samples were unevenly distributed, and thus some exposure measurements were based on a few or even single PFAS measurements. For some of the historical hotspot areas, information on levels before 2014 was obtained by personal communications. In addition, the estimated exposure does not account for differences in individual water consumption patterns and other non-water related PFAS exposures. Still, the effort was made to increase the accuracy of the maternal exposure based on the available data. Among other things, we used long-term migratory patterns when calculating drinking water related PFAS exposure. We also estimated the cumulative maternal serum levels of PFAS and besides considering water PFAS levels we also used measured background PFAS serum levels sampled among pregnant Swedish women during the corresponding year as far back to 2002. Toxicokinetic models are commonly used to account for not only the exposure, but also the delayed elimination of the substances from the body (i.e. their half-life). The latter is highly relevant in the present study, due to differences in half-lives between the PFAS, and because this age-group are prone to changing residences, which could affect their PFAS drinking water content and the subsequent exposure estimations. The toxicokinetic model can also be used to account for the background PFAS exposure, which was particularly relevant herein, due to the lack of information on PFAS exposure from other sources than the drinking water. The background PFAS exposure information originates from two Swedish studies with similar population characteristics (Miaz et al. 2020; Shu et al. 2019). Still, it should be mentioned that PFAS background levels to a large extent originate from other sources than drinking water, and thus only areas with the highest PFAS drinking water levels will have a large impact on the total maternal PFAS level. This may contribute to uncertainties in the exposure estimates, especially in the lowest exposure category. In terms of the accuracy of water consumption, it should also be mentioned that the vast majority of the adult Swedish population consumes tap water (99.8 %) – most of the tap water being consumed at home – and bottled water consumption is very low (Säve-Söderbergh et al., 2018). Sales statistics from 2019 also support that tap water is the primary source of consumption, as Sweden had the lowest estimated bottled water consumption per capita, 10 L/person-year, compared with 118 L/person-year among the other of the 25 EU-countries included (Conway 2020). This may affect the generalizability when comparing the findings to other studies with a similar study design. Still, assumptions linked to aggregate data usage and limited data on other sources of exposure may introduce uncertainties and unknown exposure misclassification. For future research, we recommend putting more effort into improving exposure information.

The study has several important strengths worth highlighting. This is one of the largest studies yet to assess the association between PFAS, GDM, hypertension and preeclampsia. This is also one of the few studies to use a locality-linked exposure approach, but where the estimated exposure accounts for water PFAS levels, maternal migratory patterns, as well as year-specific background PFAS levels among pregnant women. We also considered the most relevant confounders at an individual level. In addition, as the study is register-based, most data come from health care or governmental administrative databases, reducing any selection associated with recruitment of participant and assure accurate information since only a limited amount of data are based on self-reports. Due to decades of publicly funded antenatal and delivery care in Sweden and compulsory reporting into the registers, the registers have a coverage close to 100 % of all completed pregnancies in Sweden (Källén and Källén 2003; Ludvigsson et al. 2016). This considered, there is still a risk that the outcome may be underreported to some extent, as not all mothers are regularly monitored for GDM and hypertension. In addition, for some mothers there were missing data for BMI and smoking status. As data also originates from antenatal care all over the country, there may be differences between care facility that may affect the data quality. In addition, despite our effort to adjust for most potential confounding factors, we cannot rule out some residual or unmeasured confounding, like family history of or unmeasured diseases. Regional subdivision by zip codes is sometimes used to adjust for contextual confounding. We observed, however, no indications of contextual confounding in multilevel modelling including some area-level indicators. Thus, further regional subdivisions were not considered relevant to avoid over-adjustment, and because we had good information on confounders at the individual level.

In conclusion, in the present study we observed inverse, non-monotonic associations for PFAS4 and GDM. No clear association for hypertension and preeclampsia, although some individual PFAS were also associated with hypertension or preeclampsia, both direct and inverse.

CRediT authorship contribution statement

Melle Säve-Söderbergh: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Irina Gyllenhammar:** Writing – review & editing, Writing –

original draft. **Tessa Schillemans:** Writing – review & editing, Formal analysis. **Emelie Lindfeldt:** Writing – review & editing, Data curation. **Carolina Vogs:** Writing – review & editing, Formal analysis. **Carolina Donat-Vargas:** Writing – review & editing, Formal analysis. **Emilie Helte:** Writing – review & editing. **Emma Ankarberg:** Writing – review & editing. **Anders Glynn:** Writing – review & editing. **Lutz Ahrens:** Writing – review & editing, Data curation. **Agneta Åkesson:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Funding acquisition, Data curation, 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.2025.109415.

Data availability

The data that has been used is confidential.

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