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Per- and polyfluoroalkyl substances in drinking water and hypertensive disorders of pregnancy in the United States during 2013–2015

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Background: Per- and polyfluoroalkyl substances (PFAS) widely exist in the environment and human bodies. Contaminated drinking water is one of the major exposure pathways for humans. Previous studies found weak or moderate associations between PFAS and hypertensive disorders of pregnancy (HDP).

Methods: We obtained the number of births and counts of HDP cases for singleton births multiply stratified by county, maternal age, race, education, smoking status, and parity from CDC WONDER, and PFAS water concentrations from EPA UCMR3 data in the United States during 2013–2015. We used binomial regression on the multiply stratified HDP data to produce equal effect estimates and standard errors to those that would be derived from using individual-level data on binary HDP status and demographic covariates in logistic regression.

Results: After adjusting for demographic covariates, we found small but statistically significant positive associations between HDP and population-weighted average water concentrations (ng/L) of all four PFAS: Odds ratio (OR) = 1.009, 95% CI = (1.001, 1.016) per IQR increase in perfluorooctanoic acid (PFOA); 1.030, 95% CI = (1.021, 1.040) per IQR increase in perfluorooctane sulfonate (PFOS); 1.008, 95% CI = (1.005, 1.011) per IQR increase in perfluoroheptanoic acid (PFHpA); 1.007, 95% CI = (1.004, 1.010) per IQR increase in perfluorohexane sulfonic acid (PFHxS), and 1.032, 95% CI = (1.022, 1.042) per IQR increase in the sum of four PFAS. Further adjustment for coexposures reversed the effect of PFOA from positive to inverse, and attenuated the effects of PFOS and PFHxS toward the null. After drinking water to serum concentration conversions, our effect estimates for PFOA, PFOS, and PFHxS are similar to previous studies.

Conclusions: We found a weak positive association between the PFAS mixture and HDP, although the generalizability is subject to inherent limitations of the public-available datasets.

Keywords: PFAS; Public water supplies; HDP, PE, PIH

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Introduction

Per- and polyfluoroalkyl substances (PFAS) are a large group of synthetic chemicals that exist widely in the environment. Contaminated drinking water, seafood, packaged fast food, daily consumer products (nonstick cookware, stain-resistant carpeting, and water repellent clothing), dust, and air are the major exposure pathways for humans.[1–3] Among nearly 5,000 types of PFAS, PFOA, and PFOS are the two most extensively produced and studied chemicals, both of which have attracted extensive attention from the scientific and regulatory community.[4] In laboratory-based animal studies, PFOA and PFOS have shown the potential for developmental toxicity

What this study adds

In this article, we examined associations between PFAS detections in public water supplies and hypertensive disorders of pregnancy (HDP) in the United States during 2013–2015. PFAS water concentrations used in this study are free of reverse causality and/or physiological confounding compared with PFAS serum measurements. In addition, we were able to explore the association between PFAS and HDP more comprehensively by including some understudied PFAS chemicals (i.e., PFHxS and PFHpA), and by taking coexposures into account. We found a small but statistically significant positive association between HDP and population-weighted average concentrations of all four PFAS (PFOA, PFOS, PFHpA, and PFHxS) and the sum of PFAS concentrations in public water supplies. Overall, our study is the first nationwide statistical analysis in the United States on PFAS in public water supplies and HDP.

and reproductive effects,[5] but there are fewer studies of these health effects in humans.

Hypertensive disorders of pregnancy (HDP) complicate approximately 5%–10% of pregnancies in the United States. HDP includes both pregnancy-induced hypertension (PIH; or gestational hypertension) and preeclampsia (PE),[6–10] the latter of which is defined as new-onset hypertension combined with proteinuria ($\geq$ 300 mg of protein excretion in a 24-hour urine collection) after 20 weeks of gestation.[11] Modest state-level variation has been observed for HDP in the United States.[12]

Most epidemiological studies on PFAS and HDP separated PE and PIH, and many focused on the effects of PFOA and PFOS only, while fewer studies investigated the potential effects of PFHxS and PFHpA. Among the previous studies, Savitz et al[13] found a significant positive association with an adjusted odds ratio (AOR) of 1.16 (95% CI = 1.03, 1.30) per interquartile range (IQR) increase in natural log PFOA between PE and PFOA based on historical exposure reconstruction with Bayesian time-dependent calibration; Wikström et al[14] found a significant positive association between PE and PFOS with an AOR of 1.53 (95% CI = 1.07, 2.20) per $\log_2$ unit increase in PFOS; Huang et al[15] found significant positive associations between perfluorobutane sulfonic acid (PFBS) and PE (AOR = 1.81, 95% CI = [1.03, 3.17] per ln unit) and overall HDP (AOR = 1.64, 95% CI = [1.09, 2.47] per ln unit). Rylander et al[16] found a significantly higher risk of PE comparing the third quartile to the first quartile of serum PFHxS (AOR = 1.67, 95% CI = 1.02, 2.74), Borghese et al[7] found a significant positive association between PE and PFHxS (AOR = 1.32, 95% CI = [1.03, 1.70] per $\log_2$ unit increase in plasma PFHxS concentration), and Darrow et al[17] found significant positive associations between PFOA, PFOS, and PIH (AOR = 1.27, 95% CI = [1.05, 1.55] per natural log unit increase in PFOA; AOR = 1.47, 95% CI = [1.06, 2.04] per log unit increase in PFOS). The other studies only found weakly or moderately insignificant positive or inverse associations between PFAS and PE, PIH, or HDP.[18–22]

The inconsistent findings in previous studies may be due to the variation in study design, study population, case definition, exposure assessment, the timing of blood sampling, exposure level, restriction to nulliparous or not, covariates and coexposure adjusted in the statistical models, statistical methods, etc. For example, some studies collected blood samples before or early in pregnancy,[7,14,16,17,21,22] while others collected blood samples in midpregnancy,[20] at delivery or after pregnancy.[15,18] Different from the studies that used measured serum PFAS concentrations, Savitz et al[13,19] analyzed the associations with PE and PIH based on environmentally modeled water and serum PFOA concentrations. HDP can adversely affect kidney function during pregnancy, leading to decreased glomerular filtration rate (GFR)[23–27] and increased serum PFAS concentrations.[28,29] Thus, the observed association between PFAS and HDP could be due to reverse causality in the studies with measured biomarkers, particularly those that sampled blood in midpregnancy or later.

During 2013–2015, the US Environmental Protection Agency (EPA) completed nationwide monitoring of six PFAS (PFOA, PFOS, PFHpA, PFHxS, perfluorononanoic acid [PFNA], and PFBS) at 4,908 public water systems (PWSs) under the third Unregulated Contaminant Monitoring Rule (UCMR3). The UCMR3 dataset is the most comprehensive data on PFAS in US public water supplies, covering all PWSs serving more than 10,000 people and a representative sample of 800 PWSs serving less than 10,000 people.[30] Overall, approximately 241 million people were served by the PWSs monitored under UCMR3.[31] During 2013–2015, PFAS was detected in 1.6% of water samples and 4% of PWSs,[32] which served 16.5 million US residents.[33] With 90% of the US population being served by public water systems,[34] UCMR3 provides an important publicly available data source for researchers to investigate the health effects of PFAS. Based on UCMR3, Hurley et al[35] found significantly higher PFOA and PFOS concentrations in California women who resided in areas with detectable levels of PFOA and PFOS in public drinking water compared with those without detectable levels. Zhu and Bartell[36] found a significant inverse association between the sum of PFAS and birthweight in the counties exposed to PFAS in drinking water in UCMR3.

Multiple US studies have investigated the associations between PFAS and HDP in communities with PFAS water contamination in West Virginia and Ohio, which are often referred to as "C8 Project" or "C8 Studies."[13,17–19,37] These are some of the largest available studies on this topic, but they also had some important limitations. First, some studies used self-reported PE without validation by medical records, which may be subject to recall bias.[13,18] Second, Stein et al[18] is restricted to pregnancies occurring in 5 years before the mother's serum PFOA measurement, that is, their exposure assessment occurred after the outcome, which is a violation of temporality in epidemiology[38] and may introduce reverse causation. Because fetal transfer in pregnancy and breastfeeding after pregnancy are both important excretion pathways for PFOA in females,[39,40] the measured serum PFOA concentrations in a few years after pregnancy may not reflect the body burden of the women before pregnancy. Additionally, Savitz et al[13,19] assessed serum PFOA levels based on historical exposure reconstruction rather than actual measurements, and therefore may be subject to substantial exposure measurement error, though this approach largely avoided physiological confounding and reverse causation.[41] Darrow et al[17] used a prospective study design with most pregnancies conceived after serum PFOA measurements, and was therefore not subject to the same concerns about temporality and historical exposure reconstruction as the other studies; these authors reported significant positive associations between PIH and PFOA and PFOS (AOR = 1.27, 95% CI = [1.05, 1.55] per natural log unit increase in PFOA; AOR = 1.47, 95% CI = [1.06, 2.04] per natural log unit increase in PFOS); and subanalyses restricted to the births conceived after serum measurements were consistent with the main results, yet with a stronger positive association between PIH and PFOS.[17]

Although recent studies in other countries incorporated some understudied PFAS chemicals, such as PFNA, PFHpA, perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoA), perfluoroundecanoic acid (PFUA), PFHxS, and PFBS,[7,14–16,20–22] the US C8 studies only investigated one or two PFAS chemicals: PFOA and/or PFOS,[13,17–19] and Nolan et al[37] used water service category (exclusively served by Little Hocking Water Association; partially served by Little Hocking Water Association; and not served by Little Hocking Water Association) as a crude exposure metric for PFOA. With PFOA and PFOS being gradually phased out in the United States in the last two decades, and some similarities in reported health outcomes across the class of PFAS chemicals,[9] other high use PFAS such as PFNA and PFHxS warrant investigation. Particularly, PFHxS was found to be ubiquitous in the serum of the US population during 2015–2016.[42] Using the UCMR3 data in this study, we were able to analyze the associations between PFAS and HDP more comprehensively by covering a larger population in the United States and incorporating some understudied PFAS chemicals (i.e., PFHpA and PFHxS) compared with previous studies in the United States. As an external exposure metric, PFAS water concentration is resistant to reverse causality or physiological confounding due to GFR, compared with PFAS serum concentration.[41] In addition, the CDC WONDER data we used in this study provide HDP status as recorded on birth certificates during the same years (2013–2015) covered by the UCMR3, facilitating the investigation of cross-sectional associations between PFAS in drinking water and HDP.

Methods

Study population

We obtained the number of cases of HDP and the number of births (including those who had HDP and those who did not) for singleton births throughout the United States during 2013–2015, multiply stratified by county, maternal age, bridged race, education, smoking status, and parity from CDC WONDER. In the CDC WONDER data, HDP is recorded as "pregnancy-associated hypertension" which includes diagnosis of either pregnancy-induced hypertension (PIH) or preeclampsia (PE). Following the practice in previous studies, we use the term "hypertensive disorders of pregnancy (HDP)" to represent pregnancy-associated hypertension.[6–10] We merged the HDP cases and the number of births by combination of the stratification variables, excluding births with "unknown or not stated" HDP status from this study. We merged the CDC WONDER data on HDP and risk factors with UCMR3 data on PFAS in drinking water by county, which produced complete data for 551 large counties with more than 100,000 people. Table 1 presents the complete data (8,116,974 singleton births) we obtained for these 551 counties, accounting for 70.7% of all 11,484,590 singleton births in the United States during 2013–2015. A flow chart in Figure S1; http://links.lww.com/EE/A187 shows the details of exclusions.

UCMR3 water quality data

We excluded PFNA and PFBS from this study because only 10 and four counties had detections for these two chemicals, respectively. The other four PFAS chemicals measured in UCMR3 (PFOA, PFOS, PFHpA, and PFHxS) were moderately to highly correlated with each other.[36] We examined the other water quality indicators reported by the US EPA and found that 1,4-dioxane was the only other UCMR3 chemical moderately associated with the four PFAS ($r > 0.3$).[36] A detailed description of the CDC WONDER and UCMR3 data, their limitations, and the merging process can be found in a previous paper.[36] Among the 551 counties in the merged data, 87 counties had detection for at least one of PFOA, PFOS, PFHpA, and PFHxS. The number of singleton births (2,085,035 births) in these 87 counties accounted for 18.2% of the total number of singleton births in the United States during 2013–2015.

Most counties have more than one public water supply (PWS), so we used two proxy indicators for PFAS exposure in the study: first, for the 551 counties in the complete merged data, we used the percentage of water measurements with PFAS detection by county (number of water samples with PFAS detections divided by the total number of water samples collected within the county) as the exposure indicator; second, for the 87 counties with PFAS detection in drinking water, we used the population-weighted average PFAS water concentrations by county (PWS-level average PFAS water concentrations weighted by population served by PWSs within a county) as the exposure indicator. We substituted values that were below the minimal reporting level (MRL) with MRL/$\sqrt{2}$ in these 87 counties. Detailed descriptions of these two exposure indicators and summary statistics can be found in a previous article.[36]

Table 1.

Predictors of HDP among singleton pregnancies in 551 counties in the United States, 2013–2015.

Categories	No. of births (%)	No. of HDP cases (%)
Total	8,116,974 (100)	225,450 (100)
Maternal age (years)		
<15	2,436 (0.03)	0 (0)
15–19	472,950 (5.8)	15,193 (6.7)
20–24	1,712,821 (21.1)	52,243 (23.2)
25–29	2,343,447 (28.9)	67,436 (29.9)
30–34	2,315,191 (28.5)	63,173 (28.0)
35–39	1,074,932 (13.2)	24,717 (11.0)
40–44	191,832 (2.4)	2,688 (1.2)
≥45	3,365 (0.04)	0 (0)
Race		
American Indian or Alaska Native	30,764 (0.4)	234 (0.1)
Asian or Pacific Islander	612,144 (7.5)	5,730 (2.5)
Black or African American	1,348,057 (16.6)	43,166 (19.1)
White	6,126,009 (75.5)	176,320 (78.2)
Education		
Eighth grade or less	267,206 (3.3)	3,553 (1.6)
Ninth through 12th grade with no diploma	876,616 (10.8)	19,322 (8.6)
High-school graduate or equivalent	1,905,846 (23.5)	56,436 (25.0)
Some college credit, but not a degree	1,663,504 (20.5)	56,973 (25.3)
Associate degree	571,084 (7.0)	12,377 (5.5)
Bachelor's degree	1,634,224 (20.1)	50,619 (22.5)
Master's degree	739,215 (9.1)	16,366 (7.3)
Doctorate or professional degree	198,732 (2.5)	2,005 (0.9)
Unknown or not stated	93,293 (1.2)	1,346 (0.6)
Excluded	167,254 (2.1)	6,453 (2.9)
Smoking status		
No	7,428,369 (91.5)	216,518 (96.0)
Yes	365,603 (4.5)	980 (0.4)
Not reported	261,560 (3.2)	7,651 (3.4)
Unknown or not stated	61,442 (0.8)	301 (0.1)
Parity		
First	3,272,130 (40.4)	140,393 (62.3)
Second	2,570,880 (31.8)	45,247 (20.1)
Third and over	2,251,921 (27.8)	39,513 (17.5)
Unknown or not stated	22,043 (0.3)	297 (0.1)

Statistical analyses

We assumed the outcome variable, the number of HDP cases within each stratum, follows a binomial distribution with the number of Bernoulli trials equal to the number of births within each stratum (n) and probability of HDP equal to P. We ran generalized linear models to examine the association between HDP and PFAS in drinking water using the *glm* function in R (version 4.1.0), where we specified the family as "binomial," the number of trials as the number of births (n), "success" as having HDP (Y), and "failure" as not having HDP (n-Y). Although the outcome variable HDP is reported at the group level, because the binomial distribution is an aggregation of independent Bernoulli trials, using multiple-stratified data in binomial regression has the same likelihood function and produces the same results (effect estimates and standard errors) as we would get using individual-level data for the binary outcome variable in logistic regression, in which each individual birth is assumed to be a single Bernoulli trial with "success" representing having HDP and "failure" representing not having HDP. In both types of analyses, the logit of the probability of HDP (P) is modeled as a linear function of the explanatory variables. A simple example with simulated data in the Supplemental Digital Content; http://links.lww.com/EE/A187 shows the code to fit the equivalent *glm* models in R based on individual-level and multiple-stratified data, which can be extended to include interactions terms. However, in this study, we are limited to county-level exposure metrics, which may produce different results from using individual-level exposure information (e.g., PFAS measurements at each person's home and workplace).

We excluded the births with "Unknown or not stated" or "Excluded" education level, smoking status, and parity in the 551 counties (shown in Table 1) from statistical analyses. We ran three sets of binomial regression models, using the two types of exposure indicators of PFAS separately. In the crude model, we examined the association between PFAS and HDP only. In the adjusted model, we examined the association while adjusting for maternal age, race, education, smoking status, and parity. In the adjusted coexposure model, we adjusted for coexposures including the other three PFAS and 1,4-dioxane in addition to the demographic covariates. We checked the

linearity assumptions of binomial/logistic regressions by visually inspecting the scatter plots between continuous PFAS predictors and logit of HDP variable, which showed that PFAS variables are all quite linearly associated with the HDP outcome in logit scale (Figures S2 and S3; http://links.lww.com/EE/A187). We evaluated the multicollinearity by examining the generalized variance-inflation factors (GVIF) and GVIF^(1/(2*df)), where df is the degrees of freedom associated with the term.[43] We found GVIF^(1/(2*df)) < 3 for all terms in the adjusted coexposure models using the two types of exposure indicators of PFAS, demonstrating no multicollinearity in the adjusted co-exposure models (Tables S1 and S2; http://links.lww.com/EE/A187). We exponentiated the effect estimates from the binomial model output to obtain odds ratios measuring the associations between PFAS and HDP. The results derived from using the two exposure indicators are shown in Tables 2 and 3, respectively.

Using the steady-state serum to drinking water conversion factors of 118:1 for PFOA, 129:1 for PFOS, and 202:1 for PFHxS derived from literature-based one-compartment pharmacokinetic models,[44] we converted the concentrations of PFOA, PFOS, and PFHxS in drinking water into the expected serum concentrations after long-term consumption of tap water. We explained the estimation of steady-state serum to drinking water ratios in the Supplemental Digital Content; http://links.lww.com/EE/A187. The drinking water to serum conversions of PFAS concentrations and odds ratios of HDP per μg/L increase in estimated steady-state serum PFAS concentrations in the 87 counties are reported in Table 4.

Results

Based on the first proxy indicator, water measurements with PFAS detection in 551 counties, we found a null association between HDP and PFOA, significant positive associations between HDP and PFOS, PFHpA, and PFHxS. Adjusting for demographic covariates partly explained the associations between HDP and PFOS, and PFHpA, thus attenuating the effect estimates toward the null. Additional adjustments for coexposures further attenuated the positive association between PFOS and HDP toward the null, changed the effects for PFOA and PFHpA to the inverse, and increased the effect size in the positive direction for PFHxS (Table 2 and Figure 1).

The IQRs for the second proxy indicator, population-weighted average PFAS water concentration in 87 counties, are shown in Table 3. Based on the second proxy indicator, we found small but statistically significant positive associations between each of the four PFAS and HDP in the crude and adjusted models. Adjusting for demographic covariates partly explained the associations between HDP and PFOS, and PFHpA, slightly attenuating the effect sizes towards the null. Additional adjustments for coexposures changed the effect of PFOA from null to inverse. We also observed a significant positive association between the sum of four PFAS and HDP, which is robust to adjustments for demographic covariates and the coexposure 1,4-dioxane (Table 3 and Figure 2).

Using steady-state serum to drinking water ratios of 118:1 for PFOA, 129:1 for PFOS, and 202:1 for PFHxS derived from literature-based pharmacokinetic models,[44] we converted the population-weighted average water concentrations (ng/L) into the expected serum concentrations (μg/L) after long-term consumption of tap water. The estimation of steady-state serum to drinking water ratios are explained in the Supplemental Digital Content; http://links.lww.com/EE/A187. The average serum concentrations after the drinking water to serum conversion are 1.7 μg/L for PFOA, 3.8 μg/L for PFOS, and 4.4 μg/L for PFHxS. The effect estimates for PFOA, PFOS, and PFHxS after adjusting for demographic covariates are shown in Table 4, which are reversed from positive to inverse for PFOA, and attenuated toward the null for PFOS and PFHxS after further adjustments for coexposures (Table 4).

Table 2.

Odds ratio of HDP per 10% increase in water measurements with PFAS detection in 551 counties in the United States during 2013–2015 (no. of births = 7,692,730; no. of HDP cases = 215,957).

	PFOA (95% CI)	PFOS (95% CI)	PFHpA (95% CI)	PFHxS (95% CI)
Crude model[a]	1.004 (0.991, 1.018)	1.071 (1.057, 1.085)	1.036 (1.022, 1.050)	1.033 (1.019, 1.047)
Adjusted model[b]	1.002 (0.988, 1.015)	1.042 (1.029, 1.056)	1.011 (0.997, 1.025)	1.030 (1.016, 1.044)
Adjusted coexposure model[c]	0.910 (0.882, 0.938)	1.015 (0.993, 1.038)	0.973 (0.945, 1.001)	1.116 (1.083, 1.151)

[a]Crude model: association between PFAS and HDP only.

[b]Adjusted model: adjusted for maternal age (<15, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, ≥50), race (American Indian or Alaska Native, Asian or Pacific Islander, Black or African American, White), education (eighth grade or less; ninth through 12th grade with no diploma; high-school graduate or equivalent; some college credit, but not a degree; Associate degree; Bachelor's degree; Master's degree; doctorate or professional degree), smoking status (yes, no), and parity (first, second, third and over).

[c]Adjusted coexposure model: adjusted for the other three PFAS, 1,4-dioxane, and all covariates in the adjusted model.

Table 3.

Odds ratios with 95% CI of HDP per IQR (ng/L) increase in population-weighted average PFAS water concentration in 87 counties with detection of at least one of the four PFAS[a] (no. of births = 2,085,035; no. of HDP cases = 57,272).

	PFOA	PFOS	PFHpA	PFHxS	Sum of 4 PFAS
IQR	14.14–14.90	28.28–31.74	7.07–7.42	21.21–22.04	70.98–78.26
IQR difference	0.76	3.46	0.35	0.83	7.28
Crude model[b]	1.009, 95% CI = 1.001, 1.016	1.033, 95% CI = 1.024, 1.042	1.014, 95% CI = 1.011, 1.017	1.007, 95% CI = 1.005, 1.010	1.037, 95% CI = 1.027, 1.047
Adjusted model[c]	1.009, 95% CI = 1.001, 1.016	1.030, 95% CI = 1.021, 1.040	1.008, 95% CI = 1.005, 1.011	1.007, 95% CI = 1.004, 1.010	1.032, 95% CI = 1.022, 1.042
Adjusted coexposure model[d]	0.976, 95% CI = 0.965, 0.986	1.018, 95% CI = 1.003, 1.034	1.014, 95% CI = 1.010, 1.018	1.003, 95% CI = 0.999, 1.007	1.031, 95% CI = 1.021, 1.041

[a]Values that were below the MRLs were substituted with MRL/ √2.

[b]Crude model: association between PFAS and HDP only.

[c]Adjusted model: adjusted for maternal age (<15, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, ≥50), race (American Indian or Alaska Native, Asian or Pacific Islander, Black or African American, White), education (eighth grade or less; ninth through 12th grade with no diploma; High school graduate or equivalent; Some college credit, but not a degree; Associate degree; Bachelor's degree; Master's degree; Doctorate or professional degree), smoking status (yes, no), and parity (first, second, third and over).

[d]Adjusted coexposure model: adjusted for the other three PFAS, 1,4-dioxane, and all covariates in the adjusted model.

Table 4.

Drinking water to serum conversions of PFAS concentrations and odds ratios with 95% CI of HDP per µg/L increase in estimated steady-state serum PFAS concentrations after long-term consumption of tap water in 87 counties with detection of at least one of the four PFAS[a] (no. of births = 2,085,035; no. of HDP cases = 57,272).

	PFOA	PFOS	PFHpA	PFHxS
Mean of population-weighted average UCMR3 water concentration (ng/L)	14.84	30.58	7.74	22.60
Steady-state serum to drinking water ratio	118:1	129:1	-	202:1
Predicted serum concentration after drinking water to serum conversion (µg/L)	1.7	3.8	-	4.4
Crude model[b]	1.10, 95% CI = 1.01, 1.20	1.07, 95% CI = 1.05, 1.10	-	1.05, 95% CI = 1.03, 1.06
Adjusted model[c]	1.09, 95% CI = 1.01, 1.20	1.07, 95% CI = 1.05, 1.09	-	1.04, 95% CI = 1.03, 1.06
Adjusted coexposure model[d]	0.76, 95% CI = 0.67, 0.86	1.04, 95% CI = 1.01, 1.08	-	1.02, 95% CI = 0.995, 1.04

[a]Values that were below the MRLs were substituted with MRL/ $\sqrt{2}$.

[b]Crude model: association between PFAS and HDP only.

[c]Adjusted model: adjusted for maternal age (<15, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, ≥50), race (American Indian or Alaska Native, Asian or Pacific Islander, Black or African American, White), education (eighth grade or less; ninth through 12th grade with no diploma; High school graduate or equivalent; Some college credit, but not a degree; Associate degree; Bachelor's degree; Master's degree; Doctorate or professional degree), smoking status (yes, no), and parity (first, second, third and over).

[d]Adjusted coexposure model: adjusted for the other three PFAS, 1,4-dioxane, and all covariates in the adjusted model.

Discussion

To our knowledge, our analyses of 8,116,974 US singleton births during 2013–2015 uses the most comprehensive database for estimating of the associations between HDP and four common PFAS (i.e., PFOA, PFOS, PFHpA, and PFHxS) in public water supplies. We found a null association between HDP and the detection of PFOA, and small positive associations between HDP and detections of PFOS, PFHpA, and PFHxS after adjusting for demographic covariates. Further adjusting for coexposures (the other three PFAS and 1,4-dioxane) changed the effect estimates differently for different PFAS chemicals.

Among the 2,085,035 singleton births in the 87 counties with exposure to PFAS in drinking water, we observed significant positive associations between HDP and population-weighted average water concentrations of all four PFAS and the sum of four PFAS, after adjusting for demographic covariates. Although further adjustment for coexposures (PFOS, PFHpA, PFHxS, and 1,4-dioxane) reversed the effect of PFOA from positive to inverse, exposure amplification bias due to residual confounding

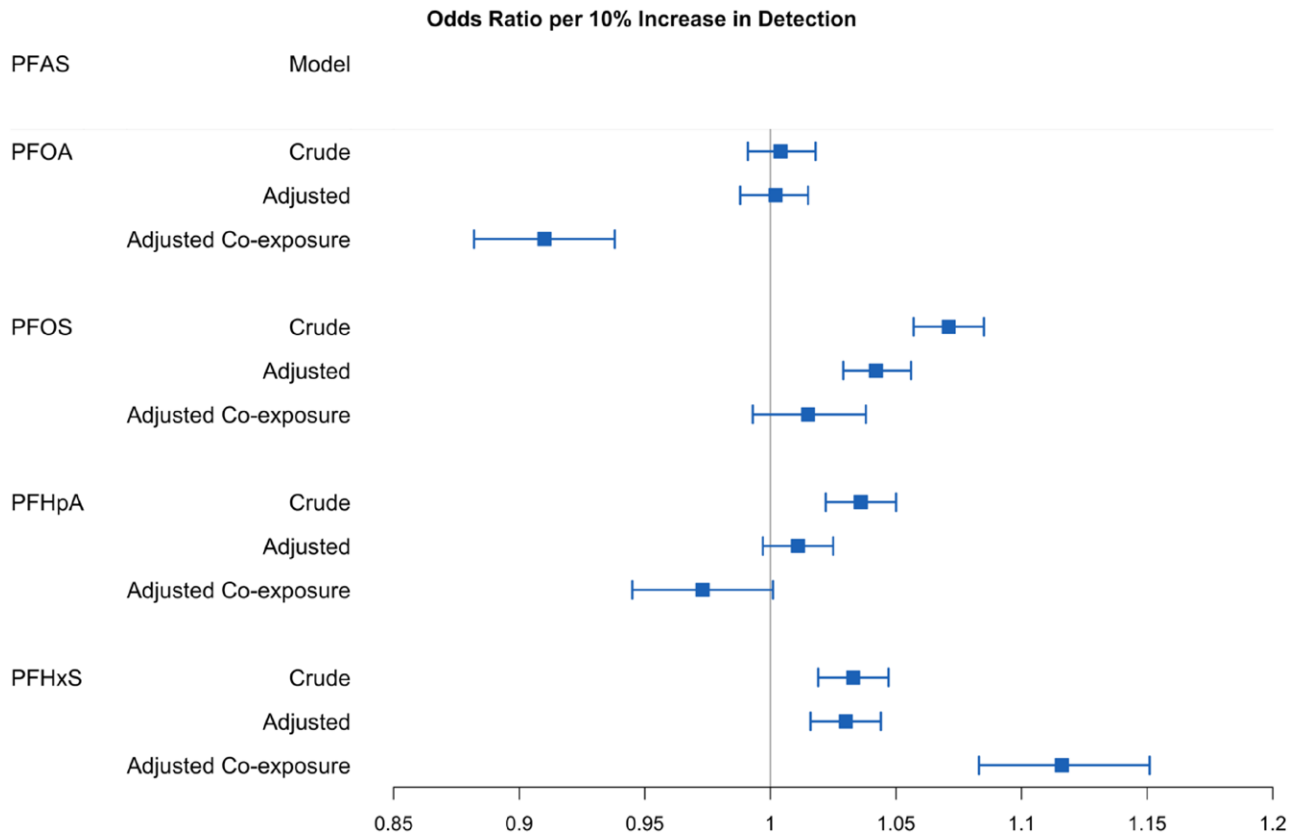

Figure 1. Odds ratio (95% CI) of HDP per 10% increase in water measurements with PFAS detection in 551 counties in the United States during 2013–2015. Crude model: association between PFAS and HDP only. Adjusted model: adjusted for maternal age (<15, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, ≥50), race (American Indian or Alaska Native, Asian or Pacific Islander, Black or African American, White), education (eighth grade or less; ninth through 12th grade with no diploma; high school graduate or equivalent; some college credit, but not a degree; Associate degree; Bachelor's degree; Master's degree; Doctorate or professional degree), smoking status (yes, no), and parity (first, second, third, and over). Adjusted coexposure model: adjusted for the other three PFAS, 1,4-dioxane, and all covariates in the adjusted model.

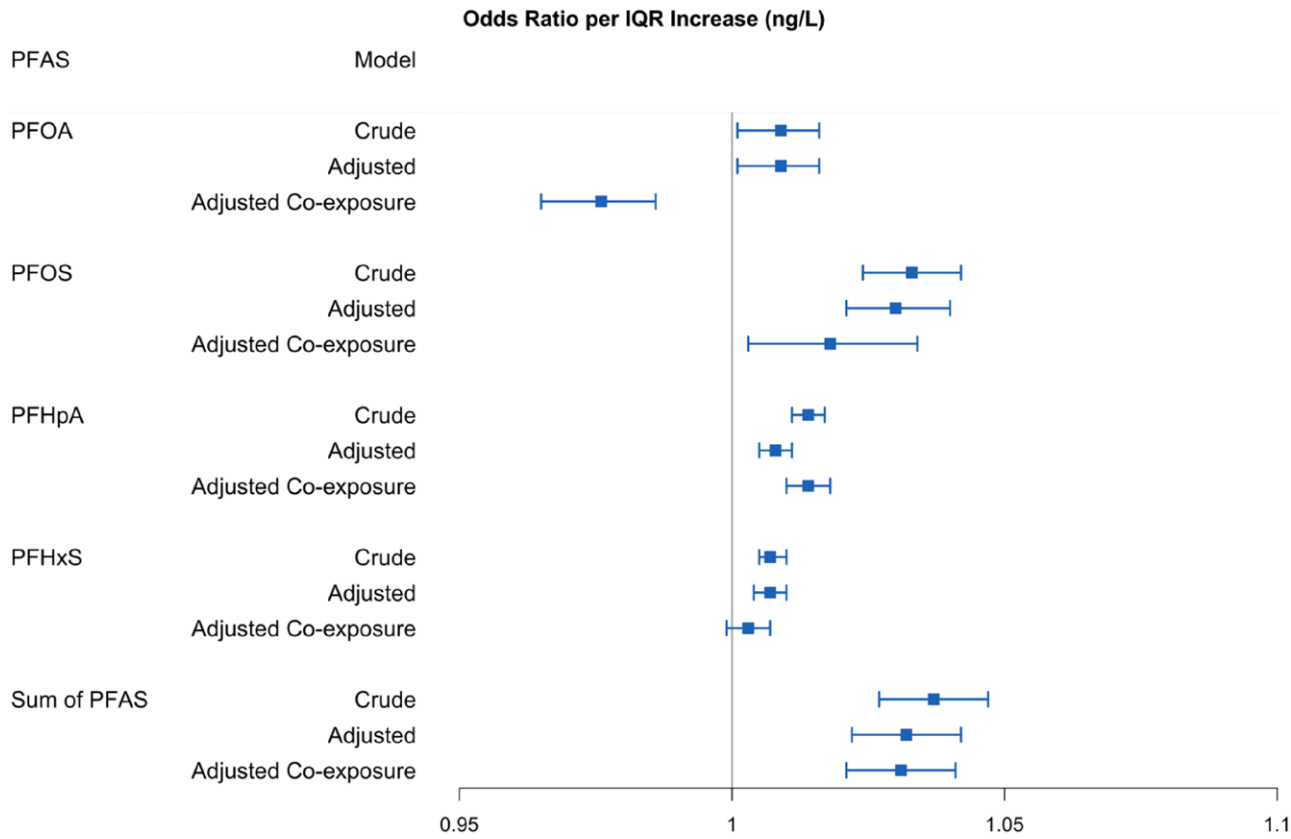

Figure 2. Odds ratio (95% CI) of HDP per IQR (ng/L) increase in the population-weighted average PFAS water concentration (ng/L = ppt = 10^{-3} μg/L) in the 87 counties. Using MRL/ $\sqrt{2}$ substitution for the nondetections. Crude model: association between PFAS and birthweight only. Adjusted model: adjusted for maternal age (<15, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, ≥50), race (American Indian or Alaska Native, Asian or Pacific Islander, Black or African American, White), education (eighth grade or less; ninth through 12th grade with no diploma; high school graduate or equivalent; some college credit, but not a degree; associate degree; bachelor's degree; master's degree; doctorate or professional degree), smoking status (yes, no), and parity (first, second, third, and over). Adjusted coexposure model: adjusted for the coexposures (the other three PFAS and 1,4-dioxane; or 1,4-dioxane only for the model includes the sum of PFAS), and all covariates in the adjusted model.

could occur when investigating correlated exposure mixtures with common sources in the same model.[45]

To facilitate the comparisons with other studies that used serum PFAS concentrations as the exposure metric, we also used steady-state serum to drinking water ratio to convert the population-weighted average PFAS water concentrations to the predicted serum concentrations after long-term consumption of tap water. After the conversion, our effect estimates for PFOA (AOR = 1.09, 95% CI = [1.01, 1.20] per μg/L), PFOS (1.07, 95% CI = [1.05, 1.09] per μg/L), and PFHxS (1.04, 95% CI = [1.03, 1.06] per μg/L) after adjusting for demographic covariates are similar to the weakly/moderately positive effect estimates found in most previous studies.[7,13,15,16,18,19,21,22]

Strengths of our study include a large sample size of 8,116,974 US singleton births that represents 71% of all singleton births in the United States during 2013–2015, information on the counties and states of the deliveries, HDP status based on birth records, and availability of multiply stratified data on HDP and key demographic covariates, equivalent to individual-level data on those variables. Particularly, the multiply stratified data structure allows the use of binomial regression to derive equivalent effect estimates and standard errors as using individual-level data on HDP and demographic covariates in logistic regression; and the large sample size provides sufficient statistical power and allows for precise quantifications of the effect estimates of PFAS exposure using two different exposure metrics. We also used two approaches to measure PFAS exposure, which produced similar results: null associations for PFOA in the crude and adjusted models, yet inverse associations for PFOA in the adjusted coexposure model; positive associations for PFOS in the crude and adjusted models, and null association for PFOS in the adjusted coexposure model; and small positive associations for PFHxS in the crude and adjusted models. The similarities in these two approaches further add credibility in our findings.

Our study also has some limitations. First, data suppression, de-identification, and some missingness in CDC WONDER restricted our analyses to 551 and 87 large counties in the United States with populations ≥100,000, respectively, for the two sets of analyses using different exposure metrics, which limits our ability to generalize the results to the entire United States.[36] Also, birth certificates may capture HDP information imperfectly in the CDC database, although a previous validation study concluded that HDP is "reported with a reasonable level of accuracy" in birth and hospital discharge data.[46] Second, the reported detections of PFAS in drinking water were dependent on the minimal reporting limits used in UCMR3, which likely underestimated the presence of PFAS in US water systems[31] and may have introduced some measurement error in our averaged water concentrations. Out of the 551 large counties covered in this study, only 87 counties had detections for at least one of the four PFAS, including 58 counties with detections for PFOA, 49 counties with detections for PFOS, 48 counties with detections for PFHpA, and 38 counties with detections for PFHxS. We also did not have individual-level information on type of water consumed to account for the use of bottled water, private well water, or public drinking water. Third, although we fit three sets of models (crude model, adjusted model, and adjusted coexposure

model) to better explore the associations between HDP and each PFAS chemical, we cannot rule out potential uncontrolled or incompletely controlled confounding, which may bias our results. Adjusting for education, in particular, shifted the parameter estimates more than other sociodemographic variables for our analyses using the first proxy indicator for PFAS exposure (Table S3; http://links.lww.com/EE/A187), suggesting possible residual confounding if education alone may not adequately capture the effects of socioeconomic status on HDP, although additionally adjusting for education only slightly shifted the parameter estimates for our analyses using the second proxy indicator for PFAS exposure (Table S4; http://links.lww.com/EE/A187). Another limitation is our use of county-level PFAS water data, instead of individual-level measurements of PFAS in personal water or serum, which may have contributed to exposure measurement error. In addition, Borghese et al[7] found that infant sex may be an effect modifier for PFAS and HDP. We tried but did not incorporate the stratified analysis by infant sex in this study due to additional data suppression after further stratification, which led to smaller strata and the inability to obtain standard error estimates.

Conclusion

We linked two publicly available databases (CDC WONDER and EPA UCMR3) to conduct a nationwide study on PFAS water concentrations and HDP. Our results show a weak positive association between the PFAS mixture and HDP, although the generalizability is subject to inherent limitations of the two datasets. Future studies using serum measurements of PFAS in early pregnancies would be a valuable addition to the body of research on this topic.

Conflicts of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Scott M. Bartell serves as a compensated expert witness for PFOA medical monitoring lawsuits in New Hampshire. The terms of this arrangement were reviewed and approved by the University of California, Irvine in accordance with its conflict-of-interest policies.

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