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Early-pregnancy plasma per- and polyfluoroalkyl substance (PFAS) concentrations and hypertensive disorders of pregnancy in the Project Viva cohort

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CRediT authorship contribution statement

Emma V. Preston: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing – original draft, Visualization. **Marie-France Hivert:** Methodology, Writing – review & editing, Project administration. **Abby F. Fleisch:** Methodology, Writing – review & editing. **Antonia M. Calafat:** Resources, Writing – review & editing. **Sharon K. Sagiv:** Writing – review & editing, Funding acquisition. **Wei Perng:** Methodology, Writing – review & editing. **Sheryl L. Rifas-Shiman:** Validation, Resources, Data curation, Writing – review & editing. **Jorge E. Chavarro:** Methodology, Writing – review & editing. **Emily Oken:** Conceptualization, Writing – review & editing, Project administration, Funding acquisition. **Ami R. Zota:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Tamarra James-Todd:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107335.

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Abstract

Background: Hypertensive disorders of pregnancy (HDP), defined here as hypertensive disorders with onset in pregnancy (i.e., gestational hypertension, preeclampsia, and preeclampsia superimposed on chronic hypertension), affect up to 10% of pregnancies in the United States and are associated with substantial maternal and neonatal morbidity and mortality. Per- and polyfluoroalkyl substances (PFAS) are associated with adverse cardiometabolic outcomes during pregnancy, but associations between PFAS and HDP are inconsistent and joint effects of PFAS mixtures have not been evaluated.

Methods: We studied 1,558 pregnant individuals from the Project Viva cohort, recruited during 1999–2002. We quantified concentrations of eight PFAS in plasma samples (median 9.7 weeks of gestation). Using clinical records, we calculated trimester-specific mean systolic (SBP) and diastolic (DBP) blood pressure and categorized HDP status [no HDP (normotensive & chronic hypertension), gestational hypertension, preeclampsia]. We estimated associations of individual PFAS with HDP using multinomial logistic regression and estimated associations with blood pressure using linear regression. We used Bayesian kernel machine regression (BKMR) and quantile g-computation to assess joint effects of the PFAS mixture on HDP and blood pressure measures.

Results: Four percent of participants developed preeclampsia and 7% developed gestational hypertension. We observed higher odds of gestational hypertension, but not preeclampsia, per doubling of perfluorooctanoate (PFOA) [OR = 1.51 (95% confidence interval: 1.12, 2.03)], perfluorooctane sulfonate (PFOS) [OR = 1.38 (1.04, 1.82)], and perfluorohexane sulfonate [OR = 1.28 (1.06, 1.54)] concentrations. We observed higher mean DBP per doubling of PFOA [2nd trimester (T2): 0.39 mmHg (−0.01, 0.78); 3rd trimester (T3): 0.56 mmHg (0.14, 0.98)] and PFOS [T2: 0.46 mmHg (0.11, 0.82); T3: 0.43 mmHg (0.05, 0.80)]. The PFAS mixture was positively associated with odds of gestational hypertension [75th vs. 50th percentile: OR = 1.14 (95% credible interval:1.03, 1.25), BKMR] and mean DBP [T2 = 0.17 mmHg (−0.06, 0.40); T3 = 0.22 mmHg (−0.03, 0.48), BKMR].

Conclusions: These findings suggest that exposure to certain PFAS may increase the odds of gestational hypertension during pregnancy, with potential implications for subsequent maternal and child health outcomes.

Keywords

PFAS; Hypertensive disorders of pregnancy; Preeclampsia; Gestational hypertension; Blood pressure

1. Introduction

Hypertensive disorders of pregnancy (HDP), defined here as hypertensive disorders with onset in pregnancy (i.e., gestational hypertension, preeclampsia/eclampsia, preeclampsia superimposed on chronic hypertension), affect 5 to 10% of pregnancies in the United States (CDC 2019; Hutcheon et al., 2011; Khedagi and Bello 2021). HDP contribute substantially to maternal and neonatal morbidity and mortality, with an estimated 14% of global maternal deaths attributed to HDP (Say et al., 2014). Beyond pregnancy, HDP are associated with poorer maternal cardiovascular health postpartum (Khedagi and Bello 2021; Mitro et al., 2020), increased risk of cardiovascular disease (Coutinho et al., 2018; Wu et al., 2020), and premature mortality (Wang et al., 2021). While established lifestyle and familial risk factors for HDP exist, these factors do not fully account for the high prevalence of HDP (Khedagi and Bello 2021). Growing evidence suggests that exposure to environmental chemicals, such as per- and polyfluoroalkyl substances (PFAS), may be associated with HDP (Erinc et al., 2021; Varshavsky et al., 2020).

PFAS are a class of fluorinated synthetic organic chemicals, which are commonly used in consumer and commercial products including upholstery and carpeting, clothing, nonstick cookware, food packaging, and firefighting foams (Sunderland et al., 2019). Some PFAS have relatively long elimination half-lives in humans ranging from 2 to 7 years, while others have half-lives on the order of days (ATSDR, 2021; Olsen et al., 2007). Because of their widespread use and environmental persistence, humans are ubiquitously exposed to PFAS through diet, drinking water, and indoor/outdoor microenvironments (Guelfo et al., 2021; Kato et al., 2011b; Sunderland et al., 2019). PFAS exposure has been associated with a wide array of adverse health effects, including dyslipidemia, hypertension, and adverse pregnancy outcomes (Fenton et al., 2021; Gao et al., 2021; Meneguzzi et al., 2021; Sunderland et al., 2019). PFAS may alter metabolic pathways during pregnancy through their interactions with certain nuclear receptors (Fenton et al., 2021; Szilagyi et al., 2020a), effects on platelet function (Minuz et al., 2021), and the placenta (Blake and Fenton 2020; Szilagyi et al., 2020a).

Previous studies examining associations of PFAS exposure with HDP are limited and have primarily focused solely on preeclampsia, rather than gestational hypertension, with inconsistent results (Erinc et al., 2021; Gao et al., 2021). Even fewer studies have evaluated the associations of PFAS with blood pressure during pregnancy, which may allow investigators to detect more subtle effects of PFAS on cardiovascular function rather than overt clinical disease (Birukov et al., 2021; Borghese et al., 2020; Vuong et al., 2021). Furthermore, while individuals are exposed to multiple PFAS, the vast majority of previous studies assessed PFAS individually and did not evaluate the potential joint effects of exposure to PFAS mixtures on HDP and blood pressure. Given the limitations and data

gaps of prior studies, our objective was to quantify the associations of plasma concentrations of individual PFAS and PFAS mixtures in early pregnancy with gestational hypertension and preeclampsia, as well as average blood pressure in the second and third trimesters, in a large prospective pregnancy cohort.

2. Methods

2.1. Study population and design

The study population consists of a subset of pregnant participants enrolled in the Project Viva longitudinal pre-birth cohort study. Project Viva enrolled participants during their first prenatal visit (median 9.6 weeks of gestation) between 1999 and 2002 at Atrius Harvard Vanguard Medical Associates facilities located in the Boston, Massachusetts metro area. Details on the cohort and study recruitment can be found elsewhere (Oken et al., 2015). Of the 2,128 eligible live births in Project Viva, 1,645 pregnancies had data on plasma PFAS concentrations, and of those, 1,610 had data on presence/absence of HDP. We excluded an additional 73 pregnancies for the following reasons: history of diabetes prior to pregnancy (n = 14), missing covariate data (n = 27), second Project Viva pregnancies (n = 8). The final analytic sample consisted of 1,558 pregnant participants, with similar sociodemographic characteristics compared to the full Project Viva cohort (Oken et al., 2015).

The Centers for Disease Control and Prevention (CDC) laboratory's involvement did not constitute engagement in human-participant research. All participating institutions' institutional review boards approved the study protocols and all study participants provided written informed consent.

2.2. Exposure assessment: plasma PFAS concentrations

We collected plasma samples from participants at their initial prenatal visit (median 9.7 weeks of gestation; sampling years 1999–2002) and stored them at −80 °C prior to analysis in 2013, as previously described (Sagiv et al., 2015). At the Division of Laboratory Sciences at the CDC (Atlanta, Georgia), we quantified concentrations of eight PFAS [perfluorohexane sulfonate, PFHxS; perfluorooctane sulfonate, PFOS; perfluorooctanoate, PFOA; perfluorononanoate, PFNA; perfluorodecanoate, PFDA; 2-(N-ethyl-perfluorooctane sulfonamido) acetate, EtFOSAA; 2-(N-methyl-perfluorooctane sulfonamide) acetate, MeFOSAA; perfluorooctane sulfonamide, FOSA] in the collected plasma samples using solid-phase extraction coupled with isotope dilution highperformance liquid chromatography-tandem mass spectrometry, as previously described (Kato et al., 2011a). The limits of detection were 0.2 ng/mL for PFOS and 0.1 ng/mL for all other PFAS. We replaced concentrations below the LOD with the LOD/√2. FOSA was only detected in 10% of samples and was not included in further analyses.

2.3. Outcome assessment: hypertensive disorders of pregnancy and blood pressure

For our primary outcome of hypertensive disorders of pregnancy (HDP), we abstracted clinical data on blood pressure, urine protein, and diagnostic and discharge codes related to gestational hypertension or preeclampsia from medical records as previously described (Oken et al., 2007). We defined gestational hypertension and preeclampsia following the

National High Blood Pressure Education Program's recommendations from the study time period (2000). We defined chronic hypertension as two or more elevated blood pressure measures (≥140 mmHg SBP or ≥ 90 mmHg DBP) before 20 weeks of gestation. We defined gestational hypertension as two or more elevated blood pressure measures (≥140 mmHg SBP or ≥ 90 mmHg DBP) after 20 weeks of gestation and preeclampsia as elevated blood pressure (≥140 mmHg SBP or ≥ 90 mmHg DBP) in combination with proteinuria (urine dipstick values of 1+ on two or more occasions >4 h but <7 days apart; or urine dipstick values of ≥2+ on one or more occasions) or chronic hypertension and proteinuria after 20 weeks of gestation. For the purposes of this analysis, we defined HDP to include hypertensive disorders with onset in pregnancy (i.e., gestational hypertension, preeclampsia, preeclampsia superimposed on chronic hypertension) and not chronic hypertension, as it occurs before pregnancy. We included all remaining participants, including those with chronic hypertension who did not develop preeclampsia (n = 21), in the no HDP reference group (normotensive & chronic hypertension). As a sensitivity analysis, we excluded participants with chronic hypertension from the reference group in our primary models.

As a complement to our primary categorical HDP outcomes, we calculated continuous trimester-specific mean SBP and DBP values, using all available blood pressure measures (from clinical records) in the second and third trimesters (median number of BP measures: n = 4 for 2nd trimester, n = 8 for 3rd trimester). A small number of participants had missing blood pressure data across pregnancy (n = 1, 2nd trimester; n = 7, 3rd trimester) and were excluded from those respective analyses only.

2.4. Covariate assessment

We collected participant sociodemographic and pregnancy characteristics via in person interviews and questionnaires at study visits and from medical records. Covariates of interest included participant age at enrollment, race/ethnicity, education, pre-pregnancy body mass index (BMI; kg/m^2), gestational weight gain (GWG), cigarette smoking status, parity, diet, prior breastfeeding, and household income. We calculated pre-pregnancy BMI based on self-reported weight and height. We assessed diet quality via a Dietary Approaches to Stop Hypertension (DASH) score based on first trimester food frequency questionnaire data, as previously described (Fulay et al., 2018). Both plasma PFAS concentrations and blood pressure/hypertensive outcomes may be affected by physiological changes during pregnancy (Costantine 2014; Loccisano et al., 2013). To account for these changes, we assessed markers of pregnancy hemodynamics, including estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault formula (Morken et al., 2014), as well as gestational week at blood draw and plasma albumin concentrations as markers of plasma volume expansion (Costantine 2014).

2.5. Statistical methods

To account for their skewed distributions, we $\log_2$-transformed PFAS concentrations in our analyses. We calculated descriptive statistics for demographic variables, outcome measures, and PFAS concentrations and calculated Spearman correlation coefficients to determine the correlations among PFAS. Blood pressure measures were relatively normally distributed and were left untransformed for analyses. We used multivariable multinomial logistic regression

models to estimate the associations of PFAS concentrations with the odds of gestational hypertension or preeclampsia. We used multivariable linear regression models to estimate associations of PFAS concentrations with second- and third-trimester mean SBP and DBP, fitting separate models for each PFAS. We modeled PFAS concentrations continuously (log_2-transformed) and as quartiles in separate models, in order to relax the assumption of linearity between PFAS and our outcomes. Estimates from continuous PFAS models represent the odds of HDP outcome or change in mean blood pressure per doubling of PFAS concentrations. As PFDA was detected (LOD = 0.1 ng/mL) in <50% of samples, we categorized PFDA concentrations as <0.1 ng/mL or ≥0.1 ng/mL for our models.

Based on prior evidence and directed acyclic graphs, we adjusted all statistical models for participant age at enrollment (years, continuous), race/ethnicity (non-Hispanic Black, non-Hispanic White, Hispanic, other race/ethnicity), education (college degree yes/no), cigarette smoking status (former smoker, pregnancy/current smoker, never smoker), and marital status (married or cohabitating yes/no). In subsequent models, we further accounted for additional potential confounding factors by individually adjusting for first trimester DASH score (continuous), annual household income (≤$70,000 vs. >$70,000), and pre-pregnancy BMI (kg/m^2) (continuous), as well as plasma albumin, eGFR, and gestational week at blood collection to account for potential confounding by hemodynamic factors. Adjusting for these additional covariates did not meaningfully change our results; therefore, we did not include them in our final models. There is uncertainty regarding the potential confounding role of hemodynamic factors in the relationships between prenatal PFAS concentrations and pregnancy outcomes with limited available data (Andersen et al., 2021; Dzierlenga et al., 2020). Therefore, we have included results from our primary models additionally adjusted for plasma albumin (g/dL), eGFR (mL/min/1.73 m^2), and gestational week of blood collection in supplemental tables (Supplemental Tables S1 & S2). Based on previous studies, we hypothesized that GWG could be on the causal pathway between PFAS exposure and HDP or changes in blood pressure. Therefore, we did not control for GWG in our models. Parity is a strong predictor of both preeclampsia risk and PFAS concentrations; however, studies have shown that adjusting for parity in regression models can lead to biased estimates due to issues of selective fertility brought about by previous pregnancy complications (Bakketeig and Hoffman 1979; Skjaerven and Melve 2007; Skjaerven et al., 1988). Individuals who experience complicated pregnancies are less likely to become pregnant again (Pirnat et al., 2019). Therefore, rather than controlling for parity or prior breastfeeding in our primary models, we performed sensitivity analyses where we restricted to nulliparous participants, as preeclampsia more commonly affects first pregnancies. This approach has been used and discussed in previous studies of preeclampsia (Skjaerven and Melve 2007; Skjaerven et al., 2012; Stuart et al., 2018). As we expect the issue of selective fertility to be less likely to affect subclinical outcome measures (i.e., continuous blood pressure), we performed sensitivity analyses of our primary blood pressure models additionally adjusting for parity. Additionally, twenty-four participants reported taking antihypertensive medications during pregnancy. To assess whether including these participants could be biasing our effect estimates towards the null, we performed sensitivity analyses excluding these participants from our primary blood pressure models.

We included the six PFAS detected in >50% of participants (PFOS, PFOA, PFHxS, PFNA, EtFOSAA, MeFOSAA) in our mixture analyses. We used Bayesian kernel machine regression (BKMR) to evaluate the individual and joint effects of exposure to PFAS on the odds of gestational hypertension or preeclampsia and continuous blood pressure (Bobb et al., 2018; Bobb et al., 2015). BKMR uses a kernel function to flexibly model both the overall joint effect of an exposure mixture and to estimate individual exposure-outcome associations. This method allows for potential non-linear exposure–response functions and can also be used to assess potential interactions among exposures. Additionally, the variable selection option in BKMR estimates posterior inclusion probabilities for each individual PFAS, which represent the relative importance of the PFAS to the overall mixture effect. We used the Probit extension of BKMR, BKMR-P, to model covariate-adjusted individual and joint effects of the six PFAS on dichotomous HDP outcomes (gestational hypertension vs. no HDP; preeclampsia vs. no HDP) (Bobb et al., 2018), and modeled individual and joint effects of the PFAS on continuous second and third trimester mean SBP and DBP using the base BKMR method. We $\log_2$-transformed and standardized PFAS concentrations for all BKMR models. Because BKMR is sensitive to extreme values, we excluded observations >5 SDs from the $\log_2$-PFAS means (n = 4).

To further evaluate the joint effects of the PFAS mixture on our outcomes and to test the robustness of our BKMR results, we used quantile g-computation. As previously described in detail (Keil et al., 2020), quantile g-computation is a recently developed method that uses a parametric generalized linear model-based approach combined with basic g-computation. Quantile g-computation provides an estimate of the overall effect of the exposure mixture on your chosen outcome and weights for the individual mixture components, which represent their relative contribution to the overall mixture effect. For our analyses, we specified quartiles as the quantile unit for PFAS concentrations. Therefore, the mixture effect estimate represents the odds ratio (dichotomous HDP outcomes) or change in mean blood pressure associated with a simultaneous quartile increase in all six PFAS. The weights for the individual PFAS represent the proportion of the positive or negative partial effect on the outcome, with the weights in each direction summing to 1.0. All BKMR and quantile g-computation models were adjusted for the same covariates as our primary individual PFAS models above.

We used R version 4.1.0 (R Core Team) to conduct the mixtures analyses using the "*bkmr*" (Bobb, 2017) and "*qgcomp*" (Kiel, 2021) packages and used SAS version 9.4 (SAS Institute Inc., Cary, NC) for all other analyses.

3. Results

Table 1 presents baseline participant characteristics in the full analytic study population and stratified by HDP category. Study participants were predominantly non-Hispanic White (69%), held a college degree (65%), and were married or cohabitating (91%). Based on our criteria, we categorized 106 (6.8%) participants as having gestational hypertension and 56 (3.6%) as having preeclampsia. Participants with preeclampsia were younger (mean 30.6 years) than those with no HDP (mean 31.9 years), and more likely to be nulliparous (75%

vs. 47%), non-Hispanic Black (34% vs. 15%), and to smoke during pregnancy (23% vs. 12%).

Table 2 shows plasma PFAS concentration distributions and detection frequencies for the seven PFAS included in our analyses. PFDA was detected in 45% of participant samples, while all other PFAS were detected in >98% of samples. PFOS had the highest median concentration (25.6 ng/mL), followed by PFOA (5.9 ng/mL). PFOS and PFOA concentrations were the most highly correlated ($r_s = 0.72$, $p < 0.001$), with other correlations ranging from 0.04 (PFDA:MeFOSAA) to 0.72 (PFOS:PFOA) (Supplemental Figure S3).

3.1. Associations of individual PFAS with HDP

When estimating associations of individual PFAS with categories of HDP (Table 3), we observed greater odds of gestational hypertension for each doubling in PFOS [OR = 1.38 (95% CI: 1.04, 1.82)], PFOA [OR = 1.51 (95% CI: 1.12, 2.03)], and PFHxS [OR = 1.28 (95% CI: 1.06, 1.54)] concentrations. Estimates for PFNA, EtFOSAA, and MeFOSAA were consistent in direction of effect but of slightly weaker magnitude with confidence intervals that included the null.

Estimates for PFAS modeled as quartiles showed similar patterns. For example, each increase in PFOA quartile was associated with greater odds of gestational hypertension [Q2 vs. Q1: OR = 1.21 (95% CI: 0.65, 2.27); Q3 vs. Q1: OR = 1.40 (95% CI: 0.75, 2.60); Q4 vs. Q1: OR = 2.07 (95% CI: 1.15, 3.73)]. However, PFOS associations were not monotonic [Q2 vs. Q1: OR = 2.14 (95% CI: 1.15, 3.99); Q3 vs. Q1: OR = 1.63 (95 % CI: 0.85, 3.12); Q4 vs. Q1: OR = 2.21 (95% CI: 1.19, 4.12)]. Results for preeclampsia were generally null. Results were comparable when excluding participants with chronic hypertension (n = 21) from the reference group (Supplemental Table S3).

Results from sensitivity analyses restricting to nulliparous participants (Supplemental Table S4) were similar in direction of effect, with somewhat weaker and less precise effect estimates for PFOS, PFOA, and PFNA, likely due to the smaller sample size (n = 767 vs. n = 1,558). For example, a doubling of PFOA concentrations was associated with greater odds of gestational hypertension [OR = 1.30 (95% CI: 0.86, 1.97)] as were increases in PFOA quartiles [Q2 vs. Q1: OR = 1.17 (95% CI: 0.45, 3.04); Q3 vs. Q1: OR = 1.28 (95% CI: 0.51, 3.20); Q4 vs. Q1: OR = 1.58 (95% CI: 0.65, 3.89)].

3.2. Associations of individual PFAS with blood pressure during pregnancy

When we estimated associations of concentrations of individual PFAS with mean trimester-specific blood pressure during pregnancy (Table 4), we found that participants with higher plasma PFOS concentrations had higher mean second trimester SBP [0.41 mmHg (95% CI: −0.07, 0.89) per doubling of PFOS] and third trimester SBP [0.46 mmHg (95% CI: −0.04, 0.96) per doubling of PFOS]. Each doubling in PFOA concentration was associated with a 0.62 mmHg (95% CI: 0.06, 1.18) higher mean third trimester SBP. Participants with detectable concentrations of PFDA had −0.83 mmHg (95% CI: −1.61, −0.06) lower mean second trimester and −0.79 mmHg (95% CI: −1.61, 0.03) lower mean third trimester SBP compared to participants with non-detectable PFDA concentrations.

We observed positive associations between higher PFOS concentrations and higher mean DBP in the second [0.46 mmHg (95 %CI: 0.11, 0.82) per doubling of PFOS] and third [0.43 mmHg (95 %CI: 0.05, 0.80) per doubling of PFOS] trimesters. Similarly, each doubling of PFOA concentration was associated with a 0.39 mmHg (95% CI: −0.01, 0.78) higher mean second trimester DBP and 0.56 mmHg (95% CI: 0.14, 0.98) higher mean third trimester DBP. When modeling PFAS as quartiles, moderate (Q2 vs. Q1) but not high (Q3 or Q4 vs. Q1) EtFOSAA concentrations were associated with higher mean third trimester DBP [Q2 vs. Q1: 1.04 mmHg (95% CI: 0.22, 1.87)].

Results of sensitivity analyses additionally adjusting SBP and DBP models for parity were similar in direction of association to those in our primary models. However, some effect estimates were attenuated, particularly for associations between PFOA concentrations and SBP and DBP measures (Supplemental Table S5). For example, after additionally adjusting for parity, estimates for associations between PFOA concentrations and mean third trimester DBP and SBP were weaker and confidence intervals crossed the null [e.g., mean SBP: 0.32 mmHg (95% CI: −0.25, 0.89); mean DBP: 0.25 mmHg (95% CI: −0.18, 0.68), per doubling of PFOA concentrations]. Estimates for associations between PFOS concentrations and third trimester DBP were also weakened [e.g., mean DBP: 0.29 mmHg (95% CI: −0.09, 0.66) per doubling of PFOS concentrations]. Conversely, in separate sensitivity analyses excluding participants taking antihypertensive medications resulted in similar or slightly stronger estimates for associations between PFAS concentrations and blood pressure outcomes (Supplemental Table S6). For example, high versus low (Q4. vs. Q1) concentrations of PFOA were more strongly associated with all blood pressure outcomes after excluding antihypertensive medication users [e.g., mean second trimester SBP: 1.11 mmHg (95% CI: 0.04, 2.17)].

3.3. Associations of the PFAS mixture with HDP

Fig. 1 shows the results of BKMR analyses for the overall mixture effect on the odds of gestational hypertension (Fig. 1A) and preeclampsia (Fig. 1B). Plasma concentrations of the PFAS mixture were positively associated with odds of gestational hypertension but not preeclampsia. Holding all PFAS at the 75th percentile compared to the 50th percentile was associated with 1.14 (95% credible interval: 1.03, 1.25) greater odds of gestational hypertension versus no HDP. Based on the estimated posterior inclusion probabilities (PIPs), BKMR identified PFHxS and PFOA as being the most important contributors to the overall association and both were independently associated with increased odds of gestational hypertension (Supplemental Table S7). Individual changes in PFOA and PFHxS concentrations from their 25th to 75th percentiles were associated with a respective 1.14 (95% CI: 0.97, 1.34) and 1.14 (95% CI: 1.00, 1.30) greater odds of gestational hypertension, while holding all other PFAS at their median concentrations. The other PFAS were not independently associated with gestational hypertension or preeclampsia (Supplemental Table S7). We did not observe evidence of substantial nonlinearity of the observed associations or evidence of interactions among the PFAS.

Results from quantile g-computation were similar to our BKMR results. Each quartile increase in the PFAS mixture index was associated with 1.43 (95% credible interval: 1.07,

1.90) greater odds of gestational hypertension versus no HDP. Based on the individual weights, PFOA and PFHxS were the largest contributors to the positive mixture effect (Supplemental Table S8), similar to the PIPs from BKMR. Like BKMR, we did not observe associations between the PFAS mixture and preeclampsia.

3.4. Associations of the PFAS mixture with blood pressure during pregnancy

Fig. 2 shows the results of our BKMR analysis for the overall effect of the PFAS mixture on mean second (Fig. 2A) and third (Fig. 2B) trimester SBP. We observed relatively weak positive trends of higher levels of the PFAS mixture and higher mean SBP in both trimesters [75th vs. 50th percentile: 2nd trimester, 0.18 mmHg (95% credible interval: −0.05, 0.40); 3rd trimester, 0.16 mmHg (95% credible interval: −0.12, 0.44); Supplemental Table S7)]. We observed a stronger association between PFOA concentrations and increased mean third trimester SBP [25th to 75th percentile: 0.42 mmHg (95% CI: −0.04, 0.88)] when holding all other PFAS at their median concentrations. In our BKMR analyses, we did not observe evidence of substantial nonlinearity among exposure−response functions, nor did we observe evidence of interactions among the PFAS.

Compared to associations with SBP, we observed slightly stronger positive associations between the PFAS mixture and mean second (Fig. 3A) and third (Fig. 3B) trimester DBP. Holding all PFAS at their 75th percentile compared to their 50th percentile was associated with a 0.17 mmHg (95% credible interval: −0.06, 0.40) increase in mean second trimester DBP and a 0.22 mmHg (95% credible interval: −0.03, 0.48) increase in mean third trimester DBP. Based on the PIPs, BKMR identified PFOS as being the primary contributor to the overall mixture effect on mean second trimester DBP, while PFOS and PFOA were the primary contributors to the effect on mean third trimester DBP (Supplemental Table S7). A change in the 25th to the 75th percentile of PFOS concentrations was associated with a 0.63 mmHg (95% CI: 0.11, 1.14) increase in mean second trimester DBP, while holding all other PFAS at their median. Greater PFOS and PFOA were suggestively associated with increases in mean third trimester DBP [25th to 75th percentile: PFOS, 0.33 mmHg (95% CI: −0.21, 0.88); PFOA, 0.32 (95% CI: −0.23, 0.88)].

Again, results from quantile g-computation were similar to those from BKMR analyses. The PFAS mixture index was suggestively associated with increased mean second and third trimester DBP [2nd trimester, 0.23 mmHg (95% CI: −0.13, 0.61); 3rd trimester, 0.19 mmHg (95% CI: −0.19, 0.58)], but was not associated with SBP measures (Supplemental Table S9). Similar to BKMR, quantile g-computation identified PFOS, PFOA, and PFHxS as positive contributors to the suggestive associations with both mean second and third trimester DBP (Supplemental Table S9).

4. Discussion

4.1. Summary of main results

In this prospective study, we observed significant positive associations between early pregnancy plasma PFOS, PFOA, and PFHxS concentrations and increased odds of gestational hypertension, but not preeclampsia. When analyzing PFAS as a mixture,

the individual associations with PFOA and PFHxS persisted, and we also observed a significant positive association between the PFAS mixture and increased odds of gestational hypertension. We also observed positive associations between higher concentrations of PFOS and PFOA and higher mean second and third trimester DBP. The individual associations with PFOS (2nd and 3rd trimester DBP) and PFOA (3rd trimester DBP) persisted in the mixtures analyses, where the PFAS mixture was also associated with higher mean DBP in both trimesters. Associations with SBP were generally null, except for associations of PFOA with mean SBP in second and third trimester, in both individual PFAS and PFAS mixture analyses.

4.2. Comparison to prior studies assessing individual PFAS and HDP

Previous studies evaluating PFAS exposure and HDP outcomes have reported inconsistent results, and few have assessed gestational hypertension as an independent outcome, despite potential etiological difference between gestational hypertension and preeclampsia (Dines and Kattah 2020). Similar to our study, a Canadian cohort (n = 1,739) reported positive associations of early pregnancy (mean 11.6 weeks of gestation) PFHxS and PFOS plasma concentrations with higher odds of gestational hypertension (Borghese et al., 2020); however, associations with PFOS were only observed in participants carrying male fetuses (Borghese et al., 2020). A second cohort study based in China (n = 3,220) reported a positive association between early pregnancy (median 15 weeks of gestation) serum concentrations of perfluoroheptanoate and increased odds of gestational hypertension, but the association was not present in multi-PFAS models (Huo et al., 2020). In contrast to our findings, results from a Danish cohort [n = 1,436, (Birukov et al., 2021)] reported null associations between serum PFAS concentrations in early pregnancy (median 12 weeks of gestation) and gestational hypertension or preeclampsia. However, median concentrations of PFOS, PFOA, and PFHxS were substantially lower in the Danish cohort compared to Project Viva (PFOS: 7.5 ng/mL vs. 25.6 ng/mL; PFOA: 1.7 ng/mL vs. 5.9 ng/mL; PFHxS: 0.4 ng/mL vs. 2.5 ng/mL). Overall, our results of positive associations between certain PFAS and increased odds of gestational hypertension are in line with previously reported findings.

A larger number of studies have evaluated associations between PFAS and preeclampsia, with inconsistent results. As in our study, three previous studies reported primarily null associations between PFAS and preeclampsia (Birukov et al., 2021; Huo et al., 2020; Starling et al., 2014), while others reported positive associations (Bommarito et al., 2021; Borghese et al., 2020; Huang et al., 2019; Rylander et al., 2020; Savitz et al., 2012; Stein et al., 2009; Wikström et al., 2019). Our null findings may relate to multiple factors, including the relatively small number of participants in our cohort with preeclampsia, the lack of ability to distinguish preeclampsia subtypes, or residual confounding due to other unmeasured factors. Studies of associations between PFAS and overall HDP (any preeclampsia or gestational hypertension) as an outcome have generally been null (Huo et al., 2020; Vuong et al., 2021). Despite some overlapping risk factors, preeclampsia and gestational hypertension also appear to have non-overlapping risk factors (Arvizu et al., 2020a; Arvizu et al., 2020b) and may have etiological differences (Dines and Kattah 2020). Therefore, when possible, these conditions should be studied as separate outcomes.

For both gestational hypertension and preeclampsia, studies varied widely in terms of study design including which PFAS were analyzed, sample collection (i.e., timing, matrix), outcome assessment, and geographical location. Because of physiological processes in pregnancy such as plasma volume expansion, increased glomerular filtration rate, and placental transfer, PFAS concentrations may vary during the course of pregnancy (Chen et al., 2021; Loccisano et al., 2013; Savitz 2014). Additionally, studies were conducted in different geographic locations and time periods, leading to greater variability in PFAS exposure distributions due to differences in production and use, which likely contributes to variability in reported findings for individual PFAS.

Variations in outcome assessment could also explain disparate results across studies, with some using self-report, medical diagnostic codes, medical chart review of diagnoses and blood pressure, and disparate clinical diagnostic criteria. For example, definitions of preeclampsia have varied across previous studies as preeclampsia diagnostic criteria has changed over time and varies by geographic region. We defined preeclampsia as elevated blood pressure in combination with proteinuria or chronic hypertension and proteinuria after 20 weeks of gestation, based on clinical guidance at the time of our study (2000). Recently guidance from the American College of Obstetrics and Gynecology includes a broader definition of preeclampsia, defined as elevated blood pressure in combination with (a) proteinuria or (b) one or more additional clinical features (i.e., thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, new-onset headache unresponsive to medications) (ACOG, 2020). While the majority of previous studies have used a more restricted definition of preeclampsia (i.e., hypertension + proteinuria), with or without inclusion of superimposed preeclampsia cases (Birukov et al., 2021; Bommarito et al., 2021; Huang et al., 2019; Huo et al., 2020; Starling et al., 2014; Wikström et al., 2019), Borghese et al. used the broader definition in their study and observed positive associations between PFAS and odds of preeclampsia (Borghese et al., 2020). It is possible that our observed positive associations between PFAS and odds of gestational hypertension are driven by participants who would have been included in the preeclampsia group under the broader definition. Unfortunately, we do not have access to data on the additional clinical features in order to investigate the effect of preeclampsia diagnosis on our findings. Future research on the effect of varying outcome definitions on estimated associations of PFAS with HDP could help guide interpretation of study results and increase comparability between studies.

4.3. Comparison to prior studies assessing individual PFAS and blood pressure

In our study, higher concentrations of PFOS, PFOA, and EtFOSAA were associated with higher mean second and/or third trimester DBP levels and higher concentrations of PFOA were associated with higher mean SBP levels. To our knowledge, only three previous studies have evaluated the association between PFAS and blood pressure during pregnancy, which have primarily reported similar associations to those in our study (Birukov et al., 2021; Borghese et al., 2020; Vuong et al., 2021). Similar to our study, Borghese et al. reported positive associations between concentrations of PFOA, PFHxS, and PFOS and DBP levels, as well as positive associations between concentrations of PFOA and PFHxS and SBP levels, using repeated blood pressure measures across pregnancy in a Canadian cohort (n = 1,739) (Borghese et al., 2020). The same study, reported positive associations

of concentrations of PFOA, PFOS, and PFHxS with trimester-specific SBP and DBP measures. For SBP models, PFOA and PFHxS concentrations were positively associated with higher third trimester SBP levels. However, as we observed in our study, associations were stronger between PFAS concentrations and DBP levels, with PFOA, PFOS, and PFHxS concentrations associated with higher DBP levels in all three trimesters (Borghese et al., 2020). Results from a Danish cohort (n = 1,436) showed a similar positive association between PFOS and DBP levels during pregnancy; however, they also reported an inverse association between PFHxS and SBP levels (Birukov et al., 2021). Conversely, a smaller (n = 388) U.S. based study observed null associations between early pregnancy PFAS concentrations (PFOS, PFOA, PFHxS, and PFNA) and SBP or DBP during pregnancy (Vuong et al., 2021).

As with HDP studies, there was variability in population and design across studies. The studies reporting associations between PFAS concentrations and blood pressure were all relatively large cohorts (n > 1,400), while the Vuong et al. study reporting null associations was much smaller (n = 388). Additionally, the Danish (Birukov et al., 2021) and Canadian (Borghese et al., 2020) cohorts modeled repeated blood pressure outcomes across pregnancy using linear mixed models, whereas Vuong et al. (2021) modeled single SBP and DBP measures (highest SBP and DBP > 20 weeks of gestation), and we modeled trimester-specific mean SBP and DBP, which were also assessed by Borghese et al. (2020).

4.4. Comparison to prior studies assessing PFAS mixtures and HDP and/ or blood pressure

Despite the fact that individuals are exposed to multiple PFAS, few studies have evaluated the joint effects of exposure to PFAS mixtures on either HDP or blood pressure outcomes during pregnancy. Huang et al. (2019) and Huo et al. (2020) used elastic net regression to identify individual PFAS associated with gestational hypertension, preeclampsia, and overall HDP. While elastic net can be used to identify individual PFAS-outcome associations while accounting for potential collinearity from exposure to other correlated PFAS (Friedman et al., 2010), it does not estimate joint effects of the PFAS mixture. As in our study, Vuong et al. (2021) used BKMR to model the individual and joint effects of PFAS on blood pressure and HDP, reporting null results. However, they also included concentrations of bisphenol A, polybrominated diphenyl ethers (PBDEs), and phthalate biomarkers in their mixtures analysis. Using BKMR and quantile g-computation, we observed similar associations between individual PFAS and gestational hypertension and blood pressure measures when modeling PFAS both individually and as a mixture, with a few exceptions. While PFOS, PFNA, EtFOSAA, and MeFOSAA concentrations were associated or suggestively associated with higher odds of gestational hypertension in individual models, they were not associated with gestational hypertension in our BKMR model and did not substantially contribute to the mixture effect in either BKMR or quantile g-computation analyses. This discrepancy could be due to the moderate to high correlations between these PFAS and PFOA and/or PFHxS (e.g., PFOS:PFOA, $r_s = 0.72$), which were individually associated with higher odds of gestational hypertension in BKMR analyses and identified as important contributors to the overall mixture effect on odds of gestational hypertension by both BKMR and quantile g-computation. We also observed significant joint effects of the PFAS mixture

on increased odds of gestational hypertension and higher mean DBP and SBP in our BKMR models. However, we did not observe evidence of interactions among the PFAS when modeling these associations. Future studies should further examine the joint effects of exposure to PFAS mixtures and should build on this work by incorporating repeated exposure and outcome measures.

4.5. Biological mechanisms

There are several proposed mechanisms to explain the observed effects of exposure to PFAS on HDP. While the exact cause(s) of HDP remain unknown, altered placental development likely plays a role (Dines and Kattah 2020; Rana et al., 2019). There is growing evidence that PFAS can disrupt placental function and development, potentially through activation of peroxisome proliferator-activated receptors (PPARs) (Blake et al., 2020; Blake and Fenton 2020; Holdsworth-Carson et al., 2010; Szilagyi et al., 2020a; Szilagyi et al., 2020b). Additionally, PFAS have also been shown to reduce trophoblast invasion, which could affect spiral artery remodeling and proper placental development (Szilagyi et al., 2020b). Systemic inflammation and oxidative stress are other potential mechanisms for the effects of PFAS on HDP and blood pressure (Erinc et al., 2021; Zota et al., 2018). Chronic inflammation has been associated with preeclampsia (Harmon et al., 2016), and prenatal PFAS concentrations have been associated with increased levels of the pro-inflammatory marker, interleukin 6 (Zota et al., 2018). Oxidative stress contributes to arterial damage and alters endothelial function, which are associated with increased blood pressure and HDP, and PFAS exposure can induce oxidative stress in human endothelial cells (Qian et al., 2010). In addition, there is growing evidence that individual PFAS exhibit differential toxicity, often varying by functional group and carbon chain length (Szilagyi et al., 2020b; Wolf et al., 2008), which may explain some of the observed variability in associations among PFAS. Further studies are needed to elucidate the underlying pathophysiology of the effects of PFAS on gestational hypertension and DBP, and the reasons for differential effects on SBP and preeclampsia.

4.6. Strengths and limitations

Our study has several limitations. First, despite a relatively large sample size, only a modest number of participants in our study population had preeclampsia. Therefore, we may have been underpowered to detect modest associations between PFAS and preeclampsia. Similarly, due to the small number of cases, we were unable to investigate differences in associations by preeclampsia subtype (i.e., early- vs. late-onset), which may have different underlying pathogenesis (Raymond and Peterson 2011). Second, we measured PFAS concentrations at a single timepoint in early pregnancy. However, most of the PFAS in our analysis have relatively long biological half-lives in humans and therefore these measures likely represent an individual’s exposure over years (Bartell et al., 2010; Olsen et al., 2007; Wang et al., 2018). Third, Project Viva enrolled pregnant individuals from 1999 to 2002, when PFOA and PFOS concentrations were substantially higher than they are today due to their phase-out (Kato et al., 2011b). Thus, the PFAS concentration profiles in our study may not be generalizable to similar populations today, despite being comparable to concentrations measured in the U.S. National Health and Nutrition Examination Survey during the corresponding time period (Sagiv et al., 2015). Nevertheless, long-alkyl chain PFAS continue to be well detected in more contemporary populations of

pregnant individuals (Calafat et al., 2019; Lin et al., 2021). Additionally, capturing close to peak levels of these legacy PFAS may have increased our ability to detect subtle associations between these PFAS and our outcomes. Finally, the Project Viva population consists of primarily non-Hispanic White individuals, living in the Boston, MA area with generally high educational attainment and socioeconomic status and may not be generalizable to all populations.

Despite these limitations our study has several notable strengths. First, we used a prospective design to evaluate the associations between early pregnancy PFAS plasma concentrations and HDP and blood pressure measures in a large established U.S. based pregnancy cohort. We evaluated associations with both gestational hypertension and preeclampsia, which we assessed via physician diagnosis and review of clinical laboratory and blood pressure measures. Additionally, we evaluated continuous mean trimester-specific blood pressures to evaluate more subtle changes in blood pressure during pregnancy related to PFAS concentrations. This is one of the first studies to evaluate the effects of PFAS mixtures on HDP and blood pressure during pregnancy. Using BKMR allowed us to flexibly model both individual and joint effects of exposure to six PFAS on HDP and blood pressure outcomes, while visually assessing exposure–response functions and evaluating potential interactions among PFAS. In addition, we used the novel quantile g-computation to assess the robustness of our BKMR results, and we found that results were quite similar across methods.

5. Conclusions

In this prospective cohort study, we found associations of early pregnancy plasma concentrations of PFAS and PFAS mixtures with increased DBP and greater odds of gestational hypertension, but not of preeclampsia. These findings add support to the small but growing body of evidence that exposure to certain PFAS may affect blood pressure regulation during pregnancy, with potential implications for subsequent maternal and child health outcomes. As PFAS exposure is ubiquitous and HDP are associated with substantial short- and long-term maternal and neonatal morbidity and mortality, future studies should further investigate the individual and joint effects of PFAS on maternal cardiometabolic health across the reproductive life course, and should investigate the reproducibility of these findings in diverse populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BKMR	Bayesian kernel machine regression
BMI	body mass index
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CI	confidence interval
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
EtFOSAA	2-(N-ethyl-perfluorooctane sulfonamido) acetate
FOSA	perfluorooctane sulfonamide
GWG	gestational weight gain
HDP	hypertensive disorders of pregnancy
LOD	limit of detection
MeFOSAA	2-(N-methyl-perfluorooctane sulfonamide) acetate
OR	odds ratio
PBDE	polybrominated diphenyl ether
PFAS	per- and polyfluoroalkyl substances
PFDA	perfluorodecanoate
PFHxS	perfluorohexane sulfonate
PFNA	perfluorononanoate
PFOA	perfluorooctanoate
PFOS	perfluorooctane sulfonate
PIP	posterior inclusion probability
PPAR	peroxisome proliferator-activated receptor
SBP	systolic blood pressure
SD	standard deviation
U.S.	United States

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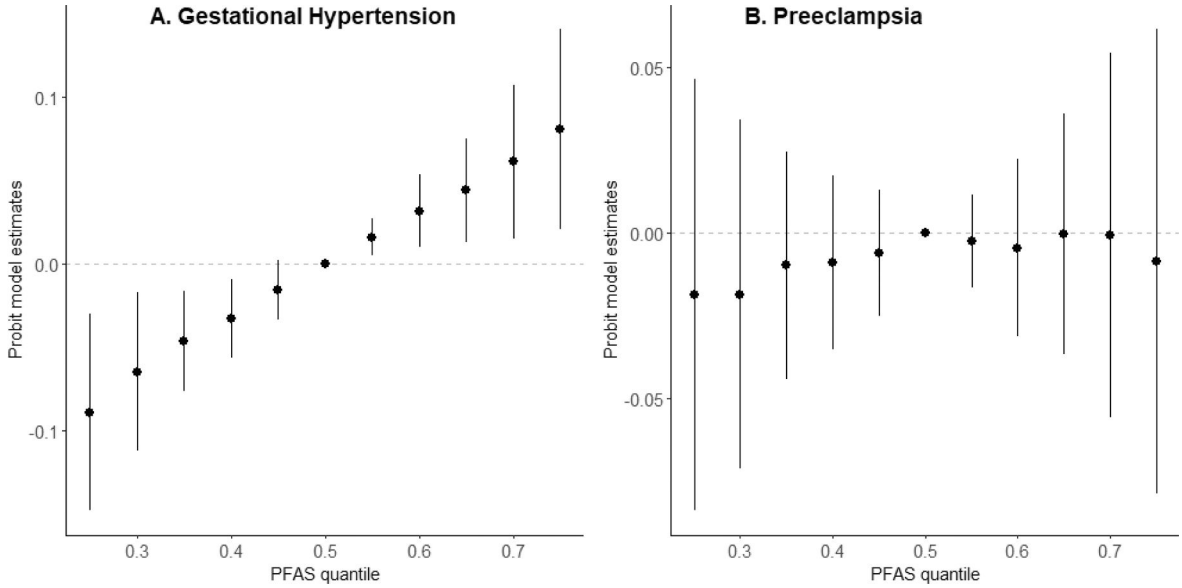

Fig. 1.

Overall effect of the per- and polyfluoroalkyl substances (PFAS) mixture on the probability of (A) gestational hypertension and (B) preeclampsia vs. no hypertensive disorders of pregnancyt (HDP) estimated by the probit extension of Bayesian kernel machine regression, adjusting for participant age at enrollment, race/ethnicity, marital status, smoking status, and education. Figures show the probit model estimates and 95% credible intervals for (A) gestational hypertension vs. normotension and (B) preeclampsia vs. normotension when all PFAS concentrations are held at certain percentiles (e.g., 25th, 45th, 75th) compared to when PFAS concentrations are held at the median.

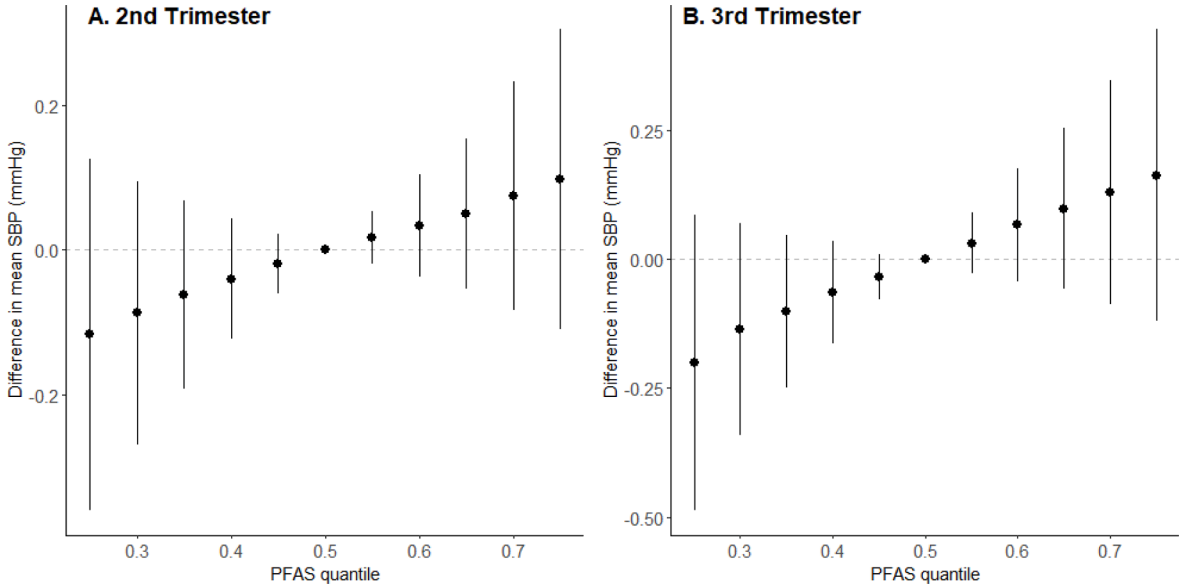

Fig. 2.

Overall effect of the per- and polyfluoroalkyl substances (PFAS) mixture on mean trimester-specific diastolic blood pressure (SBP) (mmHg), adjusting for participant age at enrollment, race/ethnicity, marital status, smoking status, and education. These plots show the estimated differences in mean (A) second trimester and (B) third trimester SBP and 95% credible intervals when concentrations of all PFAS are held at a certain percentile (e.g., 25th, 45th, 75th) compared to when all PFAS concentrations are held at the median.

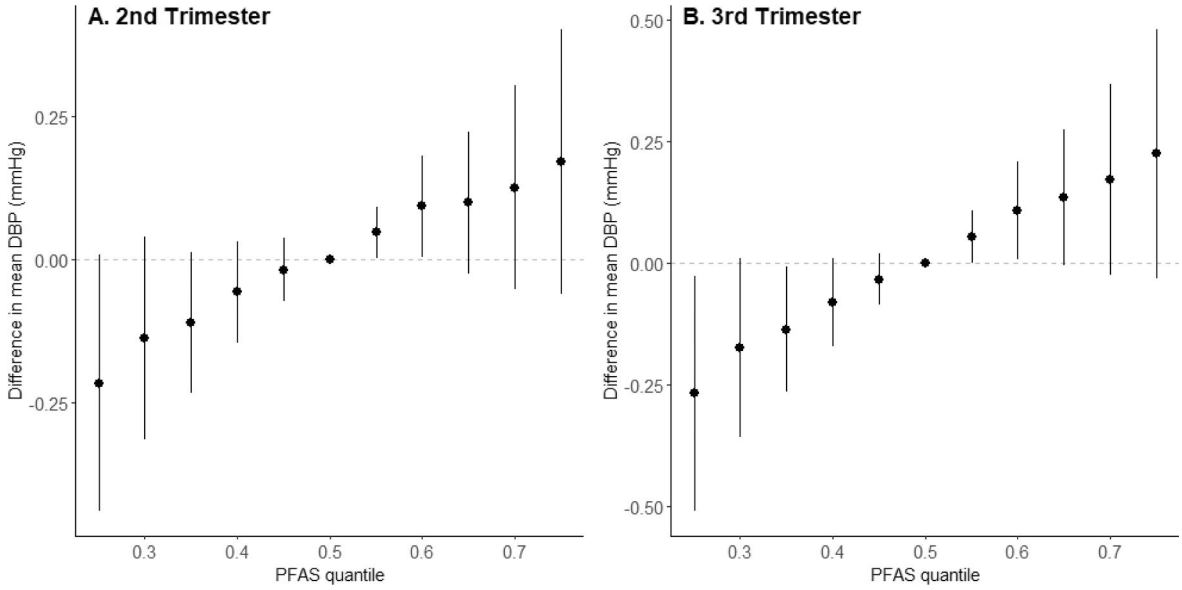

Fig. 3.

Overall effect of the per- and polyfluoroalkyl substances (PFAS) mixture on mean trimester-specific diastolic blood pressure (DBP) (mmHg), adjusting for participant age at enrollment, race/ethnicity, marital status, smoking status, and education. These plots show the estimated differences in mean (A) second trimester and (B) third trimester DBP and 95% credible intervals when concentrations of all PFAS are held at a certain percentile (e.g., 25th, 45th, 75th) compared to when all PFAS concentrations are held at the median.

Table 1

Participant characteristics and blood pressure measures in all 1,558 Project Viva participants and according to HDP category.

Characteristics	All (n = 1,558) Mean ± SD or n (%)	No HDP (n = 1,396) Mean ± SD or n (%)	Gestational hypertension (n = 106) Mean ± SD or n (%)	Preeclampsia (n = 56) Mean ± SD or n (%)
Age at enrollment (years)	31.9 ± 5.1	31.9 ± 5.1	31.3 ± 5.2	30.6 ± 6.2
Body mass index (BMI, kg/m^2)	25.0 ± 5.5	24.7 ± 5.4	25.9 ± 5.3	28.7 ± 7.1
Race/ethnicity				
Non-Hispanic Black	243 (16)	211 (15)	13 (12)	19 (34)
Non-Hispanic White	1,073 (69)	960 (69)	83 (78)	30 (54)
Hispanic	111 (7)	101 (7)	6 (6)	4 (7)
Other race/ethnicity	131 (8)	124 (9)	4 (4)	3 (5)
College degree	1,011 (65)	902 (65)	80 (75)	29 (52)
Married or cohabitating	1,419 (91)	1,275 (91)	98 (92)	46 (82)
Smoking status				
Former	292 (19)	261 (19)	23 (22)	8 (14)
During pregnancy	204 (13)	175 (12)	16 (15)	13 (23)
Never	1,062 (68)	960 (69)	67 (63)	35 (63)
Nulliparous	767 (49)	656 (47)	69 (65)	42 (75)
2nd Trimester blood pressure[a]				
No. of BP measures	4.1 ± 1.4	4.1 ± 1.4	4.0 ± 1.3	4.6 ± 1.6
Mean SBP (mmHg)	110.6 ± 7.6	109.9 ± 7.1	115.9 ± 7.4	118.0 ± 11.0
Mean DBP (mmHg)	67.6 ± 5.6	67.1 ± 5.3	71.6 ± 4.9	72.9 ± 6.5
3rd Trimester blood pressure[b]				
No. of BP measures	8.3 ± 2.4	8.2 ± 2.2	9.8 ± 3.2	8.2 ± 3.0
Mean SBP (mmHg)	113.1 ± 8.0	111.8 ± 6.6	123.5 ± 7.3	126.0 ± 12.7
Mean DBP (mmHg)	70.3 ± 6.0	69.3 ± 5.1	78.8 ± 5.4	79.4 ± 6.9

HDP, hypertensive disorders of pregnancy; SD, standard deviation; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a] Missing data, n = 1.

[b] Missing data, n = 7.

Table 2

Distribution of early-pregnancy plasma PFAS concentrations (ng/mL) in Project Viva (n = 1,558).

PFAS (ng/mL)	% detection[a]	Min	25th	Median	75th	Max
PFOS	99.8	<LOD	18.7	25.6	34.7	185
PFOA	100	0.3	4.2	5.9	7.9	36.7
PFHxS	99.3	<LOD	1.6	2.5	3.8	74.5
PFNA	98.7	<LOD	0.5	0.7	0.9	6.0
EtFOSAA	99.7	<LOD	0.7	1.2	1.9	33.6
MeFOSAA	100	0.1	1.3	1.9	3.2	29.7
PFDA	44.7	<LOD	<LOD	<LOD	0.3	3.0

Abbreviations: PFAS, per- and polyfluoroalkyl substances; PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamido) acetate; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamide) acetate; PFDA, perfluorodecanoate.

[a] Limits of detection were 0.2 ng/mL for PFOS and 0.1 ng/mL for all other PFAS.

Table 3

Covariate-adjusted[a] odds of gestational hypertension or preeclampsia for each increase in quartile and per doubling of plasma PFAS concentrations (ng/mL) compared to no hypertensive disorders of pregnancy (HDP) participants (n = 1,558).

		Gestational hypertension (n = 106) vs. No HDP (n = 1,396)[b]	Preeclampsia (n = 56) vs. No HDP (n = 1,396)[b]
PFAS		OR (95% CI)	OR (95% CI)
PFOS	Q1 (0.1–18.7)	1 (ref)	1 (ref)
	Q2 (18.8–25.6)	2.14 (1.15, 3.99)	0.99 (0.45, 2.19)
	Q3 (25.7–34.7)	1.63 (0.85, 3.12)	1.16 (0.55, 2.48)
	Q4 (34.8–185)	2.21 (1.19, 4.12)	1.04 (0.48, 2.28)
	Per doubling	1.38 (1.04, 1.82)	1.02 (0.72, 1.46)
PFOA	Q1 (0.3–4.2)	1 (ref)	1 (ref)
	Q2 (4.3–5.9)	1.21 (0.65, 2.27)	0.80 (0.36, 1.75)
	Q3 (6.0–7.9)	1.40 (0.75, 2.60)	0.87 (0.39, 1.95)
	Q4 (8.0–36.7)	2.07 (1.15, 3.73)	1.41 (0.68, 2.92)
	Per doubling	1.51 (1.12, 2.03)	1.14 (0.77, 1.69)
PFHxS	Q1 (0.1–1.6)	1 (ref)	1 (ref)
	Q2 (1.7–2.5)	0.95 (0.49, 1.81)	1.14 (0.55, 2.38)
	Q3 (2.6–3.8)	1.13 (0.62, 2.09)	1.08 (0.51, 2.29)
	Q4 (3.9–74.5)	2.06 (1.16, 3.64)	0.81 (0.35, 1.87)
	Per doubling	1.28 (1.06, 1.54)	0.89 (0.70, 1.15)
PFNA	Q1 (0.1–0.5)	1 (ref)	1 (ref)
	Q2 (0.6–0.7)	1.31 (0.78, 2.21)	1.16 (0.58, 2.31)
	Q3 (0.8–0.9)	1.51 (0.84, 2.69)	0.98 (0.42, 2.30)
	Q4 (1.0–6.0)	1.14 (0.64, 2.03)	1.20 (0.57, 2.53)
	Per doubling	1.21 (0.92, 1.59)	1.20 (0.83, 1.73)
EtFOSAA	Q1 (0.1–0.7)	1 (ref)	1 (ref)
	Q2 (0.8–1.2)	1.46 (0.80, 2.65)	0.85 (0.39, 1.88)
	Q3 (1.3–1.9)	1.82 (1.00, 3.31)	1.40 (0.67, 2.92)
	Q4 (2.0–33.6)	1.53 (0.82, 2.84)	0.80 (0.35, 1.83)
	Per doubling	1.14 (0.95, 1.37)	0.97 (0.75, 1.26)
MeFOSAA	Q1 (0.1–1.3)	1 (ref)	1 (ref)
	Q2 (1.4–1.9)	1.29 (0.72, 2.31)	2.02 (0.93, 4.42)
	Q3 (2.0–3.2)	1.26 (0.72, 2.21)	1.24 (0.55, 2.82)
	Q4 (3.3–29.7)	1.40 (0.79, 2.48)	1.34 (0.59, 3.07)
	Per doubling	1.11 (0.90, 1.36)	1.09 (0.81, 1.45)
PFDA	<0.1 ng/mL	1 (ref)	1 (ref)
	≥0.1 ng/mL	0.94 (0.63, 1.42)	0.81 (0.45, 1.46)

Abbreviations: HDP, hypertensive disorders of pregnancy; PFAS, per- and polyfluoroalkyl substances; PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamido) acetate; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamide) acetate; PFDA, perfluorodecanoate.

[a] Adjusted for age at enrollment, race/ethnicity, marital status, smoking status, education.

[b] Includes normotensive and chronic hypertensive participants.

Table 4

Covariate-adjusted[a] associations of 2nd and 3rd trimester mean blood pressure (mmHg) for each increase in quartile and per doubling of early-pregnancy plasma PFAS concentrations (ng/mL) (n = 1,557)[b].

		Mean SBP (mmHg)		Mean DBP (mmHg)	
		2nd Trimester	3rd Trimester	2nd Trimester	3rd Trimester
PFAS		Beta (95% CI)	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)
PFOS	Q1 (0.1–18.7)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
	Q2 (18.8–25.6)	0.19 (−0.87, 1.25)	0.39 (−0.73, 1.51)	0.78 (0.00, 1.57)	0.87 (0.03, 1.71)
	Q3 (25.7–34.7)	0.51 (−0.55, 1.57)	0.70 (−0.41, 1.82)	0.95 (0.17, 1.73)	0.98 (0.14, 1.82)
	Q4 (34.8–185)	0.99 (−0.08, 2.06)	1.03 (−0.09, 2.16)	0.98 (0.19, 1.77)	0.90 (0.06, 1.75)
	Per doubling	0.41 (−0.07, 0.89)	0.46 (−0.04, 0.96)	0.46 (0.11, 0.82)	0.43 (0.05, 0.80)
PFOA	Q1 (0.3–4.2)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
	Q2 (4.3–5.9)	0.63 (−0.42, 1.67)	0.29 (−0.82, 1.39)	0.22 (−0.55, 0.99)	0.27 (−0.56, 1.10)
	Q3 (6.0–7.9)	−0.46 (−1.53, 0.61)	0.03 (−1.10, 1.17)	0.09 (−0.70, 0.88)	0.31 (−0.54, 1.17)
	Q4 (8.0–36.7)	0.89 (−0.18, 1.97)	1.33 (0.20, 2.47)	0.87 (0.07, 1.66)	1.04 (0.19, 1.89)
	Per doubling	0.32 (−0.22, 0.85)	0.62 (0.06, 1.18)	0.39 (−0.01, 0.78)	0.56 (0.14, 0.98)
PFHxS	Q1 (0.1–1.6)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
	Q2 (1.7–2.5)	−0.47 (−1.54, 0.59)	−0.16 (−1.29, 0.96)	0.30 (−0.48, 1.09)	0.30 (−0.54, 1.15)
	Q3 (2.6–3.8)	−0.18 (−1.23, 0.88)	−0.21 (−1.33, 0.90)	0.62 (−0.16, 1.40)	0.28 (−0.56, 1.12)
	Q4 (3.9–74.5)	−0.44 (−1.54, 0.66)	−0.05 (−1.20, 1.11)	0.50 (−0.31, 1.31)	0.46 (−0.41, 1.33)
	Per doubling	−0.22 (−0.57, 0.13)	−0.14 (−0.51, 0.23)	0.07 (−0.19, 0.33)	0.09 (−0.19, 0.37)
PFNA	Q1 (0.1–0.5)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
	Q2 (0.6–0.7)	0.66 (−0.31, 1.62)	0.47 (−0.55, 1.50)	0.01 (−0.71, 0.72)	0.34 (−0.43, 1.10)
	Q3 (0.8–0.9)	−0.08 (−1.20, 1.05)	0.36 (−0.83, 1.55)	−0.19 (−1.02, 0.65)	0.27 (−0.63, 1.16)
	Q4 (1.0–6.0)	−0.39 (−1.42, 0.65)	0.14 (−0.95, 1.23)	−0.29 (−1.05, 0.47)	−0.14 (−0.96, 0.68)
	Per doubling	−0.27 (−0.75, 0.21)	−0.01 (−0.52, 0.50)	−0.02 (−0.38, 0.34)	0.05 (−0.33, 0.44)
EtFOSAA	Q1 (0.1–0.7)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
	Q2 (0.8–1.2)	0.35 (−0.69, 1.39)	0.77 (−0.32, 1.87)	0.55 (−0.22, 1.32)	1.04 (0.22, 1.87)
	Q3 (1.3–1.9)	−0.46 (−1.53, 0.62)	0.40 (−0.74, 1.53)	0.52 (−0.27, 1.32)	0.51 (−0.34, 1.36)
	Q4 (2.0–33.6)	0.53 (−0.56, 1.61)	0.57 (−0.58, 1.71)	0.62 (−0.18, 1.42)	0.53 (−0.33, 1.39)
	Per doubling	0.16 (−0.19, 0.51)	0.17 (−0.19, 0.54)	0.22 (−0.04, 0.48)	0.12 (−0.16, 0.40)
MeFOSAA	Q1 (0.1–1.3)	0 (ref)	0 (ref)	0 (ref)	0 (ref)
	Q2 (1.4–1.9)	0.43 (−0.64, 1.50)	0.65 (−0.48, 1.77)	0.46 (−0.33, 1.25)	0.80 (−0.04, 1.65)
	Q3 (2.0–3.2)	−0.17 (−1.20, 0.85)	0.12 (−0.96, 1.20)	0.35 (−0.40, 1.11)	0.26 (−0.55, 1.07)
	Q4 (3.3–29.7)	0.06 (−1.01, 1.13)	0.15 (−0.98, 1.28)	0.15 (−0.64, 0.95)	0.37 (−0.48, 1.22)
	Per doubling	0.01 (−0.39, 0.40)	0.14 (−0.27, 0.56)	0.06 (−0.23, 0.36)	0.19 (−0.13, 0.50)
PFDA	<0.1 ng/mL	0 (ref)	0 (ref)	0 (ref)	0 (ref)
	≥0.1 ng/mL	−0.83 (−1.61, −0.06)	−0.79 (−1.61, 0.03)	−0.24 (−0.81, 0.33)	−0.31 (−0.92, 0.31)

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; PFAS, per- and polyfluoroalkyl substances; PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; EtFOSAA, 2-(N-ethyl-perfluorooctane sulfonamido) acetate; MeFOSAA, 2-(N-methyl-perfluorooctane sulfonamide) acetate; PFDA, perfluorodecanoate.

[a] Adjusted for age, race/ethnicity, marital status, smoking status, and education.

[b] n = 1,557 for 2nd trimester and n = 1,551 for 3rd trimester.