Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

McKenzi Thompson _____

[Student's name typed] Date

Approval Sheet

Prenatal exposure to per- and poly-fluoroalkyl substances (PFAS) and associations with hypertensive disorders of pregnancy in the Atlanta African American Maternal-Child Cohort

By

McKenzi Thompson

Degree to be awarded: Master of Public Health

Epidemiology

_____ [Chair's signature]

Dr. Stephanie Eick, Ph.D., MPH

Committee Chair

Prenatal exposure to per- and poly-fluoroalkyl substances (PFAS) and associations with hypertensive disorders of pregnancy in the Atlanta African American Maternal-Child Cohort

By

McKenzi Thompson

Bachelor of Science in Biochemistry and Molecular Biology

Mills College

2021

Thesis Committee Chair: Dr. Stephanie Eick, Ph.D., MPH

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2023

Abstract

Prenatal exposure to per- and poly-fluoroalkyl substances (PFAS) and associations with hypertensive disorders of pregnancy in the Atlanta African American Maternal-Child Cohort

By McKenzi Thompson

Background/Aims: Per- and polyfluoroalkyl substances (PFAS) are environmental chemicals that are widely detected in the environment and are slow to break down. Epidemiological evidence suggests that prenatal exposure to PFAS leads to adverse birth outcomes. However, the relationship between PFAS, pregnancy complications remain largely unknown, despite biologic plausibility. Here, we examined associations between a mixture of PFAS in relation to hypertensive disorders of pregnancy in a birth cohort of African Americans.

Methods: Participants in the present study were enrolled in the Atlanta African Maternal-Child cohort (N=513). Four PFAS were measured in 1st trimester serum samples and were detected in >80% of participants. Logistic regression was used to assess associations between individual natural log transformed PFAS and hypertensive disorders of pregnancy (preeclampsia, gestational hypertension), while quantile g-computation was used to estimate mixture effects. Preeclampsia gestational hypertension were treated as separate outcomes in individual models. All models were adjusted for maternal education, maternal age, parity, and any alcohol, tobacco, or drug use.

Results: Individual PFAS were not strongly associated with gestational hypertension or preeclampsia in single pollutant or quantile g-computation models. For example, using quantile g-computation a simultaneous one quartile increase in all PFAS was associated with a non-significant reduction in odds of gestational hypertension (odds ratio= 0.86, 95% confidence interval= 0.60, 1.23).

Conclusions: Our findings suggest that PFAS are not strongly associated with hypertensive disorders of pregnancy.

Prenatal exposure to per- and poly-fluoroalkyl substances (PFAS) and associations with hypertensive disorders of pregnancy in the Atlanta African American Maternal-Child Cohort

By

McKenzi Thompson

Bachelor of Science in Biochemistry and Molecular Biology

Mills College

2021

Thesis Committee Chair: Dr. Stephanie Eick, Ph.D., MPH

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2023

Table of Contents

1.0 Introduction 2

2.0 Material and Methods 4

2.1. Study population 4

2.2. Per- and polyfluorinated Substances (PFAS) measurement 4

2.3. Hypertensive disorders of pregnancy 5

2.4. Covariates 6

2.5. Statistical analyses 6

3.0 Results 7

4.0 Discussion 9

5.0 Conclusions 12

6.0 References 13

7.0 Tables and figures 16

Table 1. Description of demographics characteristics of the Atlanta African American Maternal-Child Cohort, 2016-2020 (N=513) 16

Table 2. Distribution of serum per- and polyfluoroalkyl substances (ng/mL) concentrations in the Atlanta African American Maternal-Child Cohort (N = 513). 17

Table 3. Unadjusted and adjusted odds ratios and 95% confidence intervals for individual pregnancy complications with an interquartile range increase in serum PFAS (ng/mL) unit increase in the Atlanta African American Maternal-Child Cohort. 18

Table 4. Odds ratios and 95% confidence intervals for the association between individual pregnancy complications and the PFAS exposure mixture, estimated using quantile g-computation among pregnant persons in the Atlanta African American Maternal-Child Cohort. 19

Table 5. Weights representing the proportion of the positive and negative effect on hypertensive disorders of pregnancy in relation to a mixture of PFAS, estimated using quantile g-computation in the Atlanta African American Maternal-Child Cohort (N=513). 20

Figure 1. Spearman correlation coefficients between natural log transformed PFAS concentrations in the Atlanta African American Maternal-Child Cohort (N=513). 21

Figure 2. Adjusted odds ratios and 95% confidence intervals for hypertensive disorders of pregnancy with an interquartile range increase in serum PFAS (ng/mL) unit increase in the Atlanta African American Maternal-Child Cohort. 22

1.0 Introduction

Hypertensive disorders of pregnancy (HDP) are characterized by chronic high blood pressure during pregnancy, which manifests as gestational hypertension, preeclampsia, and/or eclampsia.[1] Gestational hypertension is defined as new-onset hypertension (blood pressure ≥ 140/90 mmHg) after 20 weeks of gestation without proteinuria,[2] while preeclampsia is diagnosed when gestational hypertension is accompanied by proteinuria or other organ dysfunction, such as impaired liver function, low platelet count, and renal insufficiency.[3] HDPs are some of the leading causes of maternal mortality in the United States (US), and have also been linked to severe maternal complications postpartum, such as heart attack and stroke.[1] Globally, preeclampsia and eclampsia impact an estimated 4.6% and 0.3% of pregnancies, respectively.[4] In the US, an estimated 11% of pregnancies are impacted by hypertensive disorders, and the prevalence is not evenly distributed across racial and ethnic groups. For example, a study using a nationally representative sample of all US hospital discharges found that 20.9% of Black women were diagnosed with HDP, compared to 12.5% of Hispanics and 9.3% of Asian/Pacific Islanders.[1] The prevalence of HDP also increases with advanced maternal age.[1] Other known risk factors for HDP include obesity, pre-existing diabetes or hypertension, family history of hypertensive disorders, and indicators of socioeconomic disadvantage (e.g., lower educational attainment).[5] However, the high prevalence of HDP is not entirely explained by these known factors,[6] which may suggest that environmental exposures play a role.

Per- and polyfluoroalkyl substances (PFAS) are a class of environmental chemicals that are of increasing public health concern. These fluorinated, man-made synthetic chemicals are commonly used in consumer and commercial products, including cleaning products, water-resistant fabrics, nonstick cookware, personal care products, and firefighting foams.[6–8] In non-

pregnant populations, elevated levels of perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), and perfluorononanoic acid (PFNA) has been linked to hypertension and high blood pressure.[9] During pregnancy, PFAS exposure has been associated with adverse pregnancy outcomes (e.g., preterm birth, low birth weight),[10,11] and a growing number of studies suggest an association with HDP.[12] For example, within the highly exposed C8 Health Study, increasing PFOA concentrations were associated with a 13% increase in odds of preeclampsia.[10] PFOS, but not other PFAS, was similarly associated with increased odds of preeclampsia in a birth cohort in Sweden.[13] Previous research has reported inconsistent results. One study found a PFAS mixture associated with gestational hypertension, but not preeclampsia, in the Project Viva cohort.[14] However, other studies have found increased levels of PFAS were linked to an elevated risk of developing preeclampsia, particularly the early-onset subtype. Additionally, higher levels of PFAS were found to be associated with increased levels of biomarkers indicating the risk of preeclampsia and suggesting a potential mechanism for the association between PFAS exposure and preeclampsia.[15]

To our knowledge, no studies have examined the associations between PFAS exposure and HDP among Black women, who are at increased risk of HDP and bear disproportionate exposures to a range of other social exposures, which may further impact health effects. To address this knowledge gap, we leveraged the Atlanta African American Maternal Child cohort, an ongoing prospective birth cohort. In the present study, we aimed to quantify the associations between maternal serum PFAS concentrations, modeled individually and as a mixture, with gestational hypertension and preeclampsia. We hypothesized that increasing PFAS exposure would be associated with increased odds of developing gestational hypertension and preeclampsia.

2.0 Material and Methods

2.1. Study population

Participants included in this analysis were enrolled in the Atlanta African American Maternal Child cohort and delivered between 2014 and 2020. This subset included participants for whom a first-trimester serum sample was available. Information regarding recruitment, retention, and data collection methods has been described elsewhere.[16] Briefly, pregnant women were recruited between 8-14 weeks gestation from two hospitals in Atlanta, Georgia. Participants were recruited from Emory University Hospital Midtown, a private hospital that provides community-based care to patients from various socioeconomic backgrounds, and Grady Memorial Hospital, a county-supported public hospital that provides services mainly to low-income or underserved populations. Inclusion criteria was as follows: 1) self-identified as a Black female; 2) between 18 and 40 years of age; 3) born in the United States; 4) singleton pregnancy; 5) English language proficiency and 6) no chronic medical condition diagnoses. Participants provided written, informed consent prior to enrollment. This study was reviewed and approved by the Institutional Review Board at Emory University.

2.2. Per- and polyfluorinated Substances (PFAS) measurement

Blood samples were obtained between 8–14 weeks gestation, centrifuged for serum, and were stored at −80 °C prior to analysis for PFAS. Levels of PFOA, PFOS, PFHxS, and PFNA were analyzed at the Children's Health Exposure Analysis Resource (CHEAR) and Human Health Exposure Analysis Resource (HHEAR) laboratories, including Wadsworth Center/New York University Laboratory Hub (Wadsworth/NYU) and the Laboratory of Exposure Assessment and

Development for Environmental Research (LEADER) at Emory University. Laboratory measurements have been cross-validated and both laboratories participate in and are certified by the German External Quality Assessment Scheme twice annually for serum PFAS quantification. Each serum sample was spiked with isotopic internal standards, treated with solid phase extraction, and analyzed using a liquid chromatographic-tandem mass spectrometric (LC-MS/MS) instrument in negative electrospray ionization mode. Multi-reaction monitoring mode was utilized for the analysis of the target compounds. Isotope dilution calibration was used to measure the target PFAS. The standard calibration curve was a matrix-matched. Bench and blind quality control samples, and blanks were analyzed alongside the unknown samples. For downstream analyses, we imputed PFAS levels below the limit of detection (LOD) with LOD/$\sqrt{2}$.[17] All PFAS were abnormally distributed, and natural log transformed.

2.3. Hypertensive disorders of pregnancy

Diagnosis of gestational hypertension and preeclampsia was determined based on medical record abstraction by trained clinical research staff. Following the American College of Obstetrics and Gynecology (ACOG) guidelines, gestational hypertension was defined as systolic blood pressure of >140 mmHg and/or a diastolic blood pressure of ≥90 mmHg after 20 weeks of gestation.[3] Preeclampsia was defined as new or worsening hypertension (≥140 mmHg systolic blood pressure or ≥90 mmHg diastolic blood pressure) and proteinuria (>300mg/24h or protein/creatinine ratio of >0.20) after 20 weeks of gestation.[3] Gestational hypertension and preeclampsia were treated as mutually exclusive outcomes. Those not diagnosed as HDP were used as the reference group in our downstream analyses.

2.4. Covariates

A standardized interview questionnaire was administered at enrollment and was used to ascertain information regarding maternal age, maternal educational attainment, prenatal health insurance type (Medicaid or private insurance), and marital status. An income-to-poverty ratio was calculated by using a combination of the number of members in the household and self-reported annual household income. Information on parity and substance use (any alcohol consumption or tobacco and marijuana use) was obtained via medical record abstraction. Early pregnancy body mass index (BMI) was calculated from measured height and weight at the first prenatal visit and was categorized as underweight (<18.5 kg/m^2), normal weight (18.5–<25 kg/m^2), overweight (25–<30 kg/m^2), and obese (≥30 kg/m^2) according to accepted World Health Organization definitions. Covariates retained in adjusted models included maternal age, education, parity, early pregnancy BMI, and substance use. These covariates were selected based on a directed acyclic graph (DAG) that was informed via a literature review and associations between exposures and outcomes in our study population.

2.5. Statistical analyses

We examined the distribution of demographic characteristics using frequencies, counts, means, and standard deviations (SDs) in the overall study population and among those with gestational hypertension and preeclampsia. We then assessed the distribution of PFAS using geometric means (GMs), geometric standard deviations (GSDs), and percentiles among the overall study population and those diagnosed with preeclampsia and gestational hypertension. We calculated Pearson correlation coefficients to estimate correlations between individual PFAS. Values range from 0-1 and higher values indicate a stronger correlation.

Logistic regression was used to unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between individual PFAS and gestational hypertension and preeclampsia, which were treated as separate outcomes in individual models. In logistic regression models, PFAS were standardized to an interquartile range (IQR) increase. To account for co-exposure to multiple PFAS, we used quantile g-computation to estimate associations between a PFAS mixture and our outcomes of interest. Quantile g-computation estimates the effect of simultaneously increasing all PFAS in the mixture by one quartile. Using this method, all PFAS included in the exposure matrix are assigned a negative and positive weight based on the direction of the independent effect. The weights sum to 1 and are an indication of relative compound importance of each PFAS in either the positive or negative direction.

3.0 Results

Among the 513 participants included in our analytic sample, 10% (N=52) were diagnosed with gestational hypertension, 7% (N=36) were diagnosed with preeclampsia, and 83% (N=425) were not diagnosed with a HDP (**Table 1**). A higher percentage of those with preeclampsia (77%) and gestational hypertension (63%) had a high education or less relative to those without a HDP (51%). Participants diagnosed with gestational hypertension (52%) and preeclampsia (67%) were also more likely to be nulliparous, as compared to those without a HDP (44%). The majority of participants with a HDP also delivered at Grady (79% for gestational hypertension, 78% for preeclampsia), compared to approximately half of those without a HDP (**Table 1**). Relative to those without a HDP, a higher percentage of those diagnosed with preeclampsia and gestational hypertension reported consuming alcohol, or using tobacco or marijuana during early pregnancy (**Table 1**).

PFOA, PFOS, PFNA, and PFHxS were detected in >90% of participants. When examining the distributions, the GM was highest for PFOA and PFOS (GM=0.63 and GM=1.91, respectively) (**Table 2**). Levels of PFOA and PFNA were slightly higher among those diagnosed with gestational hypertension relative to those who did not have a HDP (**Table 2**). In contrast, PFAS levels among those with preeclampsia were generally lower than PFAS levels among those who did not have a HDP (**Table 2**). Pearson correlation coefficients indicated that PFAS were moderately to strongly correlated with one another (**Figure 1**).

In logistic regression models, we observed that an IQR increase in each individual PFAS was not strongly associated with gestational hypertension or preeclampsia. For example, an IQR increase in PFNA was associated with a non-significant increase in odds of gestational hypertension (OR= 1.11, 95% CI= 0.77, 1.67) and preeclampsia (OR= 1.08, 95% CI= 0.71, 1.7) after adjusting for covariates (**Table 3; Figure 2**). Conversely, an IQR increase in PFOA and PFHxS was associated with a slight, non-significant reduction in odds of preeclampsia in adjusted models (OR= 0.90, 95% CI=0.64, 1.3 for PFOA; OR= 0.90, 95% CI= 0.61, 1.34 for PFHxS) (**Table 3; Figure 2**). Associations were similar in unadjusted logistic regression models (**Table 3**).

Results obtained using quantile g-computation were similar to those observed in single pollutant models. Using quantile g-computation, increasing all exposures in the PFAS mixture by one quartile was not associated with preeclampsia (OR=0.99, 95% CI=0.66, 1.48) and was associated with a non-significant decrease in odds of gestational hypertension (OR=0.86, 95% CI= 0.60, 1.23) (**Table 4**). PFHxS and PFOA were assigned negative weights in the model, including gestational hypertension as the outcome of interest (**Table 5**).

4.0 Discussion

Within a prospective birth cohort of AA women in Atlanta, Georgia, we examined the associations between early pregnancy PFAS exposure and gestational hypertension and preeclampsia. We did not observe strong associations between individual PFAS or their mixture with preeclampsia or gestational hypertension. However, we observed that a higher percentage of those diagnosed with preeclampsia and gestational hypertension had a high school education or less, and used alcohol, tobacco, or marijuana the month before pregnancy compared to those without HDP. Our results contribute to our understanding of sociodemographic risk factors for HDP among AAs.

Our study adds to the sparse body of literature assessing the impacts of PFAS exposure among African American women, who have been historically underrepresented in perinatal and environmental epidemiology studies, despite having higher rates of chemical exposures and adverse pregnancy outcomes relative to other racial and ethnic groups. Although our study found that preeclampsia and gestational hypertension were weakly and inconsistently associated with individual PFAS or a PFAS mixture, other studies have found more supportive evidence. For example, a 2022 meta-analysis of 14 studies found that PFOA, PFOS, and PFNA was associated with a significant increase in odds of preeclampsia ((OR= 1.20, 95% CI= 1.04, 1.39 for PFOA; OR= 1.23, 95% CI= 1.10, 1.38 for PFOS; and OR= 1.20, 95% CI= 1.03, 1.40 for PFNA)).[18] It is possible that the discrepancies in our results could be due to heterogeneous outcome assessment, as an analysis conducted within the LIFECODES study in Boston, Massachusetts, found that levels of PFDA and PFOS, measured in early pregnancy serum, were associated with increased odds of developing late-onset preeclampsia.[19] That study observed inconsistent associations between PFAS and early-onset preeclampsia, suggesting that there may be distinct etiologies for

preeclampsia subtypes.[19] We were unable to determine between subtypes of preeclampsia in our study due to sample size restrictions, which may explain the differences across groups and underlying study populations as participants in LIFECODES were primarily white and of higher socioeconomic status.[19] Several other studies conducted in Norway, Sweden, China, and Canada have also observed that higher levels of certain PFAS (e.g., PFOA, PFOS, and PFHxS) are linked to an increased risk of developing preeclampsia. [20,21]

Although not observed in our study, prior evidence from meta-analyses also suggests that PFAS exposure, specifically PFOA and PFHxS, is associated with increased odds of gestational hypertension.[18] These findings were confirmed with an analysis conducted within the Project Viva cohort, where increasing concentrations of PFOA, PFHxS, and PFOS, as well as a PFAS mixture, was associated with higher odds of gestational hypertension but not preeclampsia.[14] Median PFAS levels in the Project Viva cohort are higher than what was observed in our study population, which may suggest some evidence of dose-response and that higher levels of PFAS may increase the risk of gestational hypertension. Within the MIREC cohort in Canada, increasing PFOA, PFOS, and PFHxS not associated with increased odds of gestational hypertension only among those who were carrying a male fetus.[20] We were unable to look at sex as a biological variable in this analysis due to sample size limitations. Other studies have produced mixed results, as studies conducted in China find that individual PFAS and PFAS mixture are not strongly associated with gestational hypertension. [22,23] Taken together, these mixed findings reinforce the need for further research to better understand the relationships between PFAS and HDP.

An estimated 15% of women during their reproductive years are affected by HDP, and racial and ethnic disparities exist in the prevalence and outcomes of HDP.[24] This is partly due to the

increasing prevalence of obesity, other cardiometabolic risk factors, and advanced age at first pregnancy. [5] In comparison to these studies, my findings indicate that women diagnosed with gestational hypertension and preeclampsia were more likely to have a high school degree, have less than 100% income-to-poverty ratio, have public insurance, and deliver at Grady Hospital. Socioeconomic factors and healthcare accessibility appear to contribute significantly to the development of HDP. The higher incidence of HDP among women with lower incomes and public insurance may be attributed to inadequate prenatal care and limited access to appropriate medical interventions during pregnancy.[25]

We previously observed that PFAS are associated with reduced fetal growth in this study population.[26] HDP and fetal growth restriction share similar biological pathways, which suggests that a link between PFAS and HDP is biologically plausible. Possible mechanisms could be through alterations in lipid metabolism, impaired placental function, and disruptions in thyroid hormones, as we have previously observed that metabolites involved in these processes are associated with both PFAS exposure and fetal growth restriction.[26] Another possible mechanism may be through oxidative stress, as laboratory studies and preliminary epidemiologic analyses have shown that PFAS exposure can induce oxidative stress during pregnancy.[25,26] Large scale epidemiologic studies have found that elevated levels of oxidative stress are associated with increased odds of preeclampsia and preterm birth.[27] In non-pregnant adult populations, oxidative stress levels also increase among those with hypertension.[28]

Our study has a number of important strengths. First, we used a prospective cohort of AA women that are rarely the center of pregnancy outcome research. However, we acknowledge that this may limit our external generalizability to other populations. Second, PFAS was measured in serum samples obtained during early pregnancy, reducing potential confounding by pregnancy-

related hemodynamics.[15] Third, we utilized quantile g-computation to assess the mixture effects of multiple PFAS, an important advancement over prior studies focusing solely on single pollutant effects. Nonetheless, we also acknowledge our limitations, as we could not assess preeclampsia subtypes, including early or late-onset, and prior work indicates that PFAS may impact the development of late-onset preeclampsia only.[19] We also had a relatively small number of diagnosed HDP cases in our study population, which impacted our statistical power. Lastly, we did not adjust for multiple comparisons. However, we acknowledge that this is not always necessary in exploratory studies as it may increase the possibility of type II error due to low statistical power.[29]

5.0 Conclusions

Among a socioeconomically diverse cohort of AA pregnant persons in metropolitan Atlanta, Georgia, we observed that PFAS were not strongly associated with preeclampsia or gestational hypertension. It is critical that we investigate modifiable risk factors for HDP among Black women, as the prevalence of HDP has increased in recent years. Specifically, more research is needed to assess the impacts of exposure to other potential environmental toxicants that may increase the risk of HDP and consider the potential combined effects of toxic chemicals and social stress. Identifying racial and ethnic chemical susceptibilities to HDP may assist in directing research to develop interventions to lessen the likelihood of developing such conditions during pregnancy.

6.0 References

1. Ford ND, Cox S, Ko JY, et al. Hypertensive Disorders in Pregnancy and Mortality at Delivery Hospitalization — United States, 2017–2019. *MMWR Morb Mortal Wkly Rep*. 2022;71(17):585-591. doi:10.15585/mmwr.mm7117a1

2. *Hypertension in Pregnancy: Diagnosis and Management*. National Institute for Health and Care Excellence (NICE); 2019. Accessed April 11, 2023. http://www.ncbi.nlm.nih.gov/books/NBK546004/

3. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin Summary, Number 222. *Obstet Gynecol*. 2020;135(6):1492-1495. doi:10.1097/AOG.0000000000003892

4. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol*. 2013;170(1):1-7. doi:10.1016/j.ejogrb.2013.05.005

5. Umesawa M, Kobashi G. Epidemiology of hypertensive disorders in pregnancy: prevalence, risk factors, predictors and prognosis. *Hypertens Res*. 2017;40(3):213-220. doi:10.1038/hr.2016.126

6. Sunderland EM, Hu XC, Dassuncao C, Tokranov AK, Wagner CC, Allen JG. A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects. *J Expo Sci Environ Epidemiol*. 2019;29(2):131-147. doi:10.1038/s41370-018-0094-1

7. Nakayama SF, Yoshikane M, Onoda Y, et al. Worldwide trends in tracing poly- and perfluoroalkyl substances (PFAS) in the environment. *TrAC Trends Anal Chem*. 2019;121:115410. doi:10.1016/j.trac.2019.02.011

8. Mamsen LS, Björvang RD, Mucs D, et al. Concentrations of perfluoroalkyl substances (PFASs) in human embryonic and fetal organs from first, second, and third trimester pregnancies. *Environ Int*. 2019;124:482-492. doi:10.1016/j.envint.2019.01.010

9. Pitter G, Zare Jeddi M, Barbieri G, et al. Perfluoroalkyl substances are associated with elevated blood pressure and hypertension in highly exposed young adults. *Environ Health*. 2020;19(1):102. doi:10.1186/s12940-020-00656-0

10. Savitz DA, Stein CR, Bartell SM, et al. Perfluorooctanoic Acid Exposure and Pregnancy Outcome in a Highly Exposed Community. *Epidemiology*. 2012;23(3):386-392. doi:10.1097/EDE.0b013e31824cb93b

11. Meneguzzi A, Fava C, Castelli M, Minuz P. Exposure to Perfluoroalkyl Chemicals and Cardiovascular Disease: Experimental and Epidemiological Evidence. *Front Endocrinol*. 2021;12:706352. doi:10.3389/fendo.2021.706352

12. Erinc A, Davis MB, Padmanabhan V, Langen E, Goodrich JM. Considering environmental exposures to per- and polyfluoroalkyl substances (PFAS) as risk factors for

hypertensive disorders of pregnancy. *Environ Res*. 2021;197:111113. doi:10.1016/j.envres.2021.111113

13. Wikström S, Lindh CH, Shu H, Bornehag CG. Early pregnancy serum levels of perfluoroalkyl substances and risk of preeclampsia in Swedish women. *Sci Rep*. 2019;9(1):9179. doi:10.1038/s41598-019-45483-7

14. Preston EV, Hivert MF, Fleisch AF, et al. Early-pregnancy plasma per- and polyfluoroalkyl substance (PFAS) concentrations and hypertensive disorders of pregnancy in the Project Viva cohort. *Environ Int*. 2022;165:107335. doi:10.1016/j.envint.2022.107335

15. Taibl KR, Liang D, Dunlop AL, et al. Pregnancy-related hemodynamic biomarkers in relation to trimester-specific maternal per - and polyfluoroalkyl substances exposures and adverse birth outcomes. *Environ Pollut Barking Essex 1987*. 2023;323:121331. doi:10.1016/j.envpol.2023.121331

16. Corwin EJ, Hogue CJ, Pearce B, et al. Protocol for the Emory University African American Vaginal, Oral, and Gut Microbiome in Pregnancy Cohort Study. *BMC Pregnancy Childbirth*. 2017;17(1):161. doi:10.1186/s12884-017-1357-x

17. Hornung RW, Reed LD. Estimation of Average Concentration in the Presence of Nondetectable Values. *Appl Occup Environ Hyg*. 1990;5(1):46-51. doi:10.1080/1047322X.1990.10389587

18. Hirke A, Varghese B, Varade S, Adela R. Exposure to endocrine-disrupting chemicals and risk of gestational hypertension and preeclampsia: A systematic review and meta-analysis. *Environ Pollut*. 2023;317:120828. doi:10.1016/j.envpol.2022.120828

19. Bommarito PA, Ferguson KK, Meeker JD, McElrath TF, Cantonwine DE. Maternal Levels of Perfluoroalkyl Substances (PFAS) during Early Pregnancy in Relation to Preeclampsia Subtypes and Biomarkers of Preeclampsia Risk. *Environ Health Perspect*. 2021;129(10):107004. doi:10.1289/EHP9091

20. Borghese MM, Walker M, Helewa ME, Fraser WD, Arbuckle TE. Association of perfluoroalkyl substances with gestational hypertension and preeclampsia in the MIREC study. *Environ Int*. 2020;141:105789. doi:10.1016/j.envint.2020.105789

21. Huang R, Chen Q, Zhang L, et al. Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and the risk of hypertensive disorders of pregnancy. *Environ Health*. 2019;18(1):5. doi:10.1186/s12940-018-0445-3

22. Yang L, Ji H, Liang H, et al. Associations of perfluoroalkyl and polyfluoroalkyl substances with gestational hypertension and blood pressure during pregnancy: A cohort study. *Environ Res*. 2022;215(Pt 2):114284. doi:10.1016/j.envres.2022.114284

23. Huo X, Huang R, Gan Y, et al. Perfluoroalkyl substances in early pregnancy and risk of hypertensive disorders of pregnancy: A prospective cohort study. *Environ Int*. 2020;138:105656. doi:10.1016/j.envint.2020.105656

24. Garovic VD, White WM, Vaughan L, et al. Incidence and Long-Term Outcomes of Hypertensive Disorders of Pregnancy. *J Am Coll Cardiol*. 2020;75(18):2323-2334. doi:10.1016/j.jacc.2020.03.028

25. Aved BM, Irwin MM, Cummings LS, Findeisen N. Barriers to prenatal care for low-income women. *West J Med*. 1993;158(5):493-498.

26. Chang CJ, Barr DB, Ryan PB, et al. Per- and polyfluoroalkyl substance (PFAS) exposure, maternal metabolomic perturbation, and fetal growth in African American women: A meet-in-the-middle approach. *Environ Int*. 2022;158:106964. doi:10.1016/j.envint.2021.106964

27. Eick SM, Geiger SD, Alshawabkeh A, et al. Urinary oxidative stress biomarkers are associated with preterm birth: an Environmental Influences on Child Health Outcomes program study. *Am J Obstet Gynecol*. Published online November 15, 2022:S0002-9378(22)02170-6. doi:10.1016/j.ajog.2022.11.1282

28. Baradaran A, Nasri H, Rafieian-Kopaei M. Oxidative stress and hypertension: Possibility of hypertension therapy with antioxidants. *J Res Med Sci Off J Isfahan Univ Med Sci*. 2014;19(4):358-367.

29. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiol Camb Mass*. 1990;1(1):43-46.

7.0 Tables and figures

Table 1. Description of demographics characteristics of the Atlanta African American Maternal-Child Cohort, 2016-2020 (N=513)

	Gestational Hypertension (N=52)	**Preeclampsia (N=36)**	**No HDP (N=425)**
Maternal Age (years)	24 (5.0)	25 (4.7)	25 (4.9)
Maternal Body Mass Index (kg/m^2)	31 (7.2)	32 (9.2)	28 (7.6)
Marital Status			
Married/Living Together	27 (52 %)	18 (50 %)	198 (47 %)
Single	25 (48 %)	18 (50 %)	227 (53 %)
Maternal Education			
<High School	11 (21 %)	7 (19 %)	63 (15%)
High School	22 (42 %)	21 (58 %)	154 (36 %)
College Degree	14 (27 %)	6 (17 %)	130 (31%)
Graduate Degree	5 (10 %)	2 (6 %)	78 (18 %)
Income to Poverty Ratio			
<100%	22 (42 %)	24 (67 %)	178 (42 %)
100-150%	15 (29 %)	3 (8 %)	97 (23 %)
150-300%	8 (15 %)	7 (19 %)	94 (22%)
>300%	7 (13 %)	2 (6%)	56 (13 %)
Tobacco Use			
No	36 (69 %)	25 (69 %)	365 (86 %)
Yes	16 (31 %)	11 (31 %)	60 (14 %)
Alcohol Consumption			
No	44 (85 %)	30 (83 %)	378 (89 %)
Yes	8 (15 %)	6 (17 %)	47 (11 %)
Marijuana Use			
No	28 (54 %)	20 (56 %)	293 (69%)
Yes	24 (46 %)	16 (44 %)	132 (31 %)
Parity			
0	27 (52 %)	24 (67 %)	189 (44%)
1+	25 (48 %)	12 (33 %)	236 (56 %)
Health Insurance			
Public	42 (81%)	32 (89%)	330 (78%)
Private	10 (19 %)	4 (11%)	95 (22%)
Delivery Hospital			
Emory	11 (21%)	8 (22 %)	187 (44%)
Grady	41 (79 %)	28 (78 %)	238 (56 %)
Infant Sex			
Male	24 (46 %)	20 (56 %)	207 (49 %)
Female	28 (54 %)	16 (44 %)	218 (51 %)

Table 2. Distribution of serum per- and polyfluoroalkyl substances (ng/mL) concentrations in the Atlanta African American Maternal-Child Cohort (N = 513).

			Percentile				
	% Above LOD	**Geometric Mean (Geometric SD)**	**5th**	**25th**	**50th**	**75th**	**95th**
PFOA							
No HDP	97.66	0.63 (2.31)	0.12	0.45	0.7	1.06	1.69
Preeclampsia	97.22	0.6 (2.31)	0.18	0.38	0.66	1.1	1.49
Gestational Hypertension	96.15	0.66 (2.17)	0.26	0.54	0.72	0.97	1.61
PFHxS							
No HDP	97.66	1.17 (2.03)	0.32	0.82	1.25	1.75	3.58
Preeclampsia	94.44	1.12 (2.07)	0.41	0.78	1.19	1.73	3.24
Gestational Hypertension	94.23	1.03 (2.3)	0.22	0.69	0.93	1.99	3.5
PFOS							
No HDP	98.25	1.91 (2.43)	0.54	1.39	2.17	3.24	5.4
Preeclampsia	97.22	1.89 (2.39)	0.36	1.12	2.18	3.09	6.26
Gestational Hypertension	98.08	1.7 (1.99)	0.58	1.28	1.8	2.81	4.54
PFNA							
No HDP	97.08	0.26 (2.34)	0.05	0.17	0.3	0.48	0.81
Preeclampsia	94.44	0.26 (2.64)	0.05	0.15	0.36	0.56	0.76
Gestational Hypertension	96.15	0.27 (2.18)	0.08	0.19	0.3	2.81	4.54

Abbreviations: HDP, Hypertensive Disease of Pregnancy; LOD, limit of detection; SD, standard deviation.

Table 3. Unadjusted and adjusted odds ratios and 95% confidence intervals for individual pregnancy complications with an interquartile range increase in serum PFAS (ng/mL) unit increase in the Atlanta African American Maternal-Child Cohort.

	Unadjusted		**Adjusted**	
	N (cases, controls)	**OR (95% CI)**	**N (cases, controls)**	**OR (95% CI)**
PFOA				
Preeclampsia	(36, 425)	0.96 (0.7, 1.37)	(36, 425)	0.90 (0.64, 1.3)
Gestational Hypertension	(52, 425)	1.07 (0.8, 1.48)	(52, 425)	1.05 (0.78, 1.48)
PFOS				
Preeclampsia	(36, 425)	0.97 (0.73, 1.37)	(36, 425)	1.08 (0.77, 1.61)
Gestational Hypertension	(52, 425)	0.88 (0.7 1.15)	(52, 425)	1.05 (0.7, 1.21)
PFHxS				
Preeclampsia	(36, 425)	0.90 (0.63, 1.32)	(36, 425)	0.90 (0.61, 1.34)
Gestational Hypertension	(52, 425)	0.81 (0.6, 1.1)	(52, 425)	0.81 (0.59, 1.12)
PFNA				
Preeclampsia	(36, 425)	1.01 (0.68, 1.56)	(36, 425)	1.08 (0.71, 1.7)
Gestational Hypertension	(52, 425)	1.06 (0.75, 1.55)	(52, 425)	1.11 (0.77, 1.67)

Abbreviations: OR, odds ratio; CI, confidence interval.
Note: Models are adjusted for maternal age, maternal education, parity, early pregnancy BMI, and substance use.

Table 4. Odds ratios and 95% confidence intervals for the association between individual pregnancy complications and the PFAS exposure mixture, estimated using quantile g-computation among pregnant persons in the Atlanta African American Maternal-Child Cohort.

	N (cases, controls)	**OR (95% CI)**
Preeclampsia	(36, 425)	0.99 (0.66, 1.48)
Gestational Hypertension	(52, 425)	0.86 (0.60, 1.23)

Abbreviations: OR, odds ratio; CI, confidence interval.
Note: Models are adjusted for maternal age, maternal education, parity, early pregnancy BMI, and substance use.

Table 5. Weights representing the proportion of the positive and negative effect on hypertensive disorders of pregnancy in relation to a mixture of PFAS, estimated using quantile g-computation in the Atlanta African American Maternal-Child Cohort (N=513).

	Gestational Hypertension	**Preeclampsia**
PFNA	0.62	0.87
PFOS	-0.59	0.13
PFOA	0.38	-0.26
PFHxS	-0.41	-0.74

Note: models are adjusted for models are adjusted for maternal age, maternal education, parity, early pregnancy BMI and substance use.

Figure 1. Spearman correlation coefficients between natural log transformed PFAS concentrations in the Atlanta African American Maternal-Child Cohort (N=513).

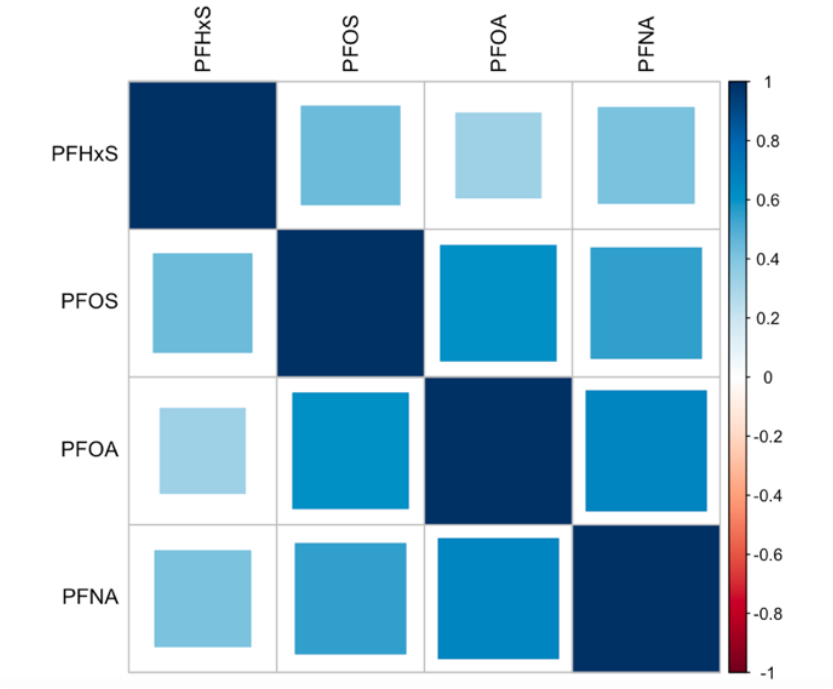
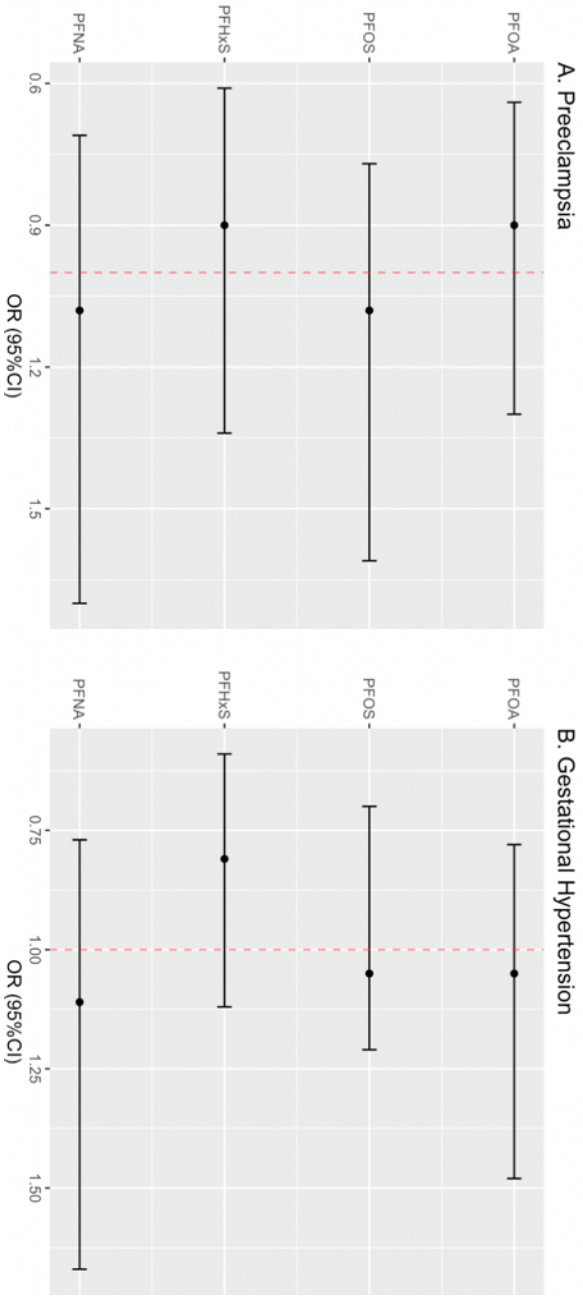


Figure 2. Adjusted odds ratios and 95% confidence intervals for hypertensive disorders of pregnancy with an interquartile range increase in serum PFAS (ng/mL) unit increase in the Atlanta African American Maternal-Child Cohort.



Abbreviations: OR, odds ratio; CI, confidence interval.

Note: models are adjusted for models are adjusted for maternal age, maternal education, parity, early pregnancy BMI and substance use.