Gestational Exposure to Phthalates, Phthalate Replacements, and Preeclampsia Diagnosis: A Longitudinal Study

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Introduction

Phthalates are a class of endocrine-disrupting chemicals found in many consumer products, including plastic packaging and fragranced personal care products.

Exposure to new phthalate replacements has been rising throughout the past decade, though it is unknown whether these replacements are safer than traditional phthalates.

Previous research has shown that pregnant persons are ubiquitously exposed to phthalates and phthalate replacements. There are racial and socioeconomic differences in personal care product use, leading to disparities in phthalate exposure between sociodemographic groups.

Preeclampsia is a hypertensive disorder of pregnancy affecting 1 in 25 pregnancies in the United States. Preeclampsia incidence has been continuously rising for decades, and Black and Indigenous persons are disproportionately affected.

A preeclamptic pregnancy increased the risk of cardiometabolic disorders and other adverse health outcomes in both the mother and the child years after parturition.

There is evidence of an association between prenatal phthalate exposure and preeclampsia, but many prior studies are not racially or socioeconomically diverse and exposure is only quantified at a single time point, often in late pregnancy.

Objective

To investigate the prospective association between gestational exposure to phthalates and their replacements throughout pregnancy and diagnosis of preeclampsia.

Human Placenta and Phthalates Study

Study Design: Prospective cohort
Recruitment: 2017-2020
Location: Norfolk, VA and Galveston, TX

Table 1: Characteristics of the study population

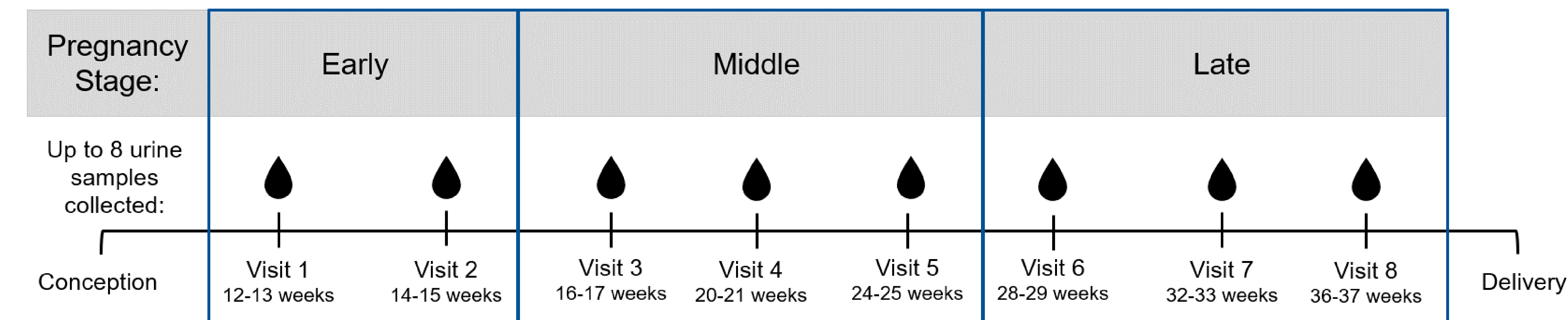| All Participants	n=291
Characteristic	n (%) or mean ± SD
Maternal Age, years	26.4 ± 5.1
Maternal BMI, kg/m³	24.82 ± 4.30
Race/Ethnicity	
Non-Hispanic Black	126 (43%)
Non-Hispanic White	113 (39%)
Hispanic	47 (16%)
Asian, Pacific Islander, or Mixed Race	5 (2%)
Annual household income	
Less than $30,000	138 (47%)
$30,000-$74,999	63 (22%)
More than $75,000	22 (8%)
Missing	68 (23%)
Highest level of education	
High school or less	127 (44%)
Some college	118 (40%)
4-year degree	37 (13%)
Missing	9 (3%)
Preeclampsia	
No	266 (91%)
Yes	25 (9%)

Methods

Figure 1: Timing of urine sample collection. Following study enrollment, n = 291 participants attended up to 8 study visits at which urine samples were collected. Two visits occurred in early pregnancy, three visits in middle pregnancy, and three visits in late pregnancy.

- Urinary concentrations of 14 phthalate metabolites and 4 replacement metabolites were quantified via LC-MS by CDC collaborators.
- After adjusting for urine specific gravity, geometric mean concentrations were calculated for early pregnancy (12-15 weeks gestation), middle pregnancy (16-25 weeks gestation), late pregnancy (26-38 weeks gestation), and overall (12-38 weeks gestation).
- Molar sums were calculated for the following phthalates: DnBP, DiBP, DEHP, and DiNP, and replacements: DEHTP and DiNCH, using the molar concentrations of their corresponding metabolites.
- Multivariate logistic regression models of preeclampsia were adjusted for maternal age, body mass index, race and ethnicity, education level, smoking, and study site.
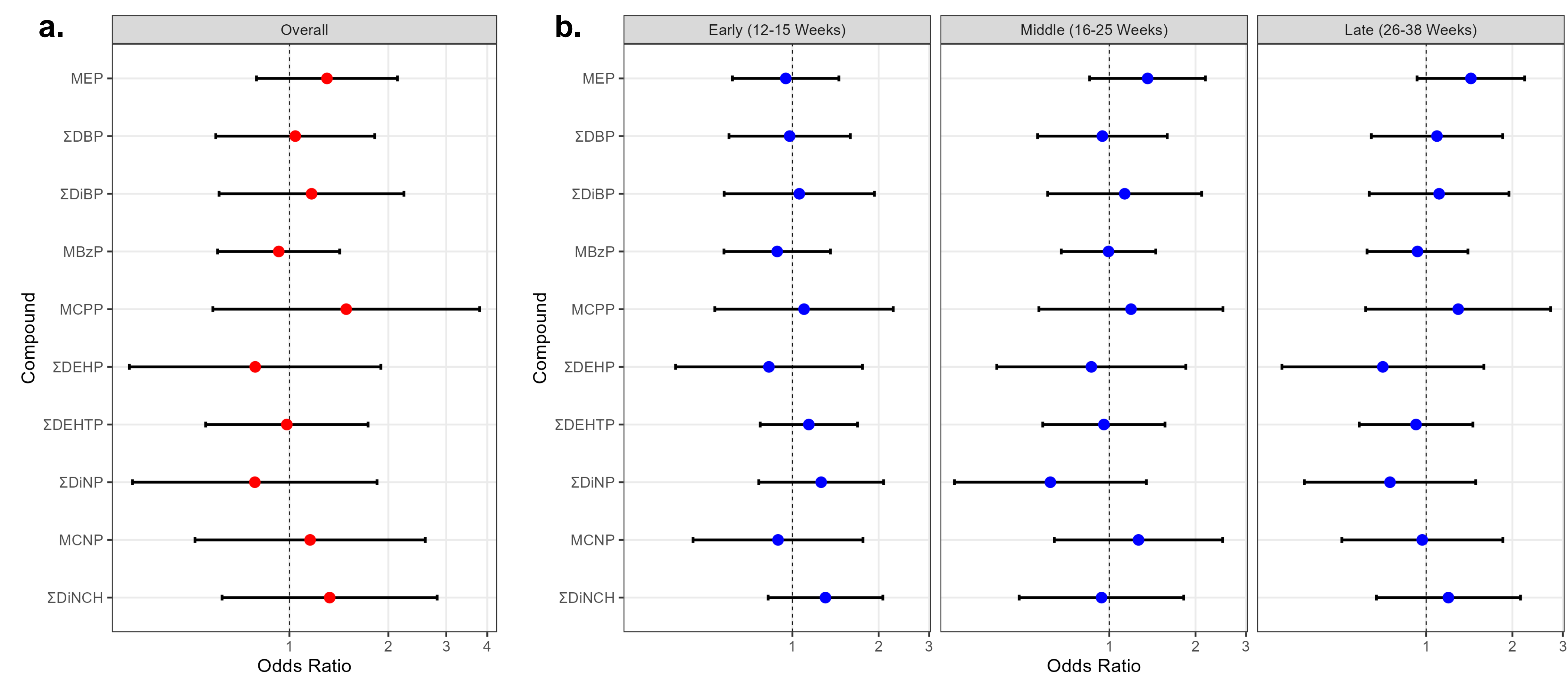
Results: Adjusted Odds Ratios of Preeclampsia

Figure 2: Adjusted odds ratios and 95% confidence intervals of preeclampsia for all phthalate and replacement metabolites.
a. Logistic regression models were adjusted for maternal age, body mass index, race and ethnicity, education level, smoking, and study site. Exposure biomarker concentrations were corrected for urine dilution using covariate-adjusted standardization plus specific gravity adjustment. For phthalates or replacements with multiple metabolites, molar sums were calculated using the molar concentrations of all metabolites (see Table 2). b. Multivariate logistic regression models were stratified by timing of sample collection.

Conclusion

In this racially and socioeconomically diverse cohort with repeated urine collections at up to 8 time points in pregnancy, we observed widespread exposure to eight phthalates and two replacements consistent with previous studies. Although not statistically significant, the odds ratios of preeclampsia increased from early to middle to late pregnancy for mono-ethyl phthalate (MEP), the primary metabolite of di-ethyl phthalate (DEP).

Exposure Biomarkers Measured

Table 2: Phthalate or replacement compounds and corresponding metabolites

	Parent Compound	Metabolite(s)
Phthalates	Diethyl phthalate (DEP)	MEP
	Di-n-butyl phthalate (DBP)	MBP, MHBP
	Di-iso-butyl phthalate (DiBP)	MiBP, MHiBP
	Benzylbutyl phthalate (BBzP)	MBzP
	Di-n-octyl phthalate (DOP)	MCPP
	Di(2-ethylhexyl) phthalate (DEHP)	MEHP, MEHHP, MEOHP, MECPP
	Di-isononyl phthalate (DiNP)	MONP, MCOP
	Di-isodecyl phthalate (DiDP)	MCNP
Replacements	Di(2-ethylhexyl) terephthalate (DEHTP)	MEHHTP, MECPTP
	1,2-Cyclohexane dicarboxylic acid, diisononyl ester (DINCH)	MHiNCH, MCOCH

Detected in >99% of samples: MEP, MEHHP, MEOHP, MECPP, MCOP, MECPTP

Detected in >90% of samples: MBP, MiBP, MHiBP, MBzP, MONP, MCNP, MEHHTP

Detected in <60% of samples: MEHP, MCOCH

Exposure biomarker concentrations that fell below the limit of detection were replaced with an imputed value.
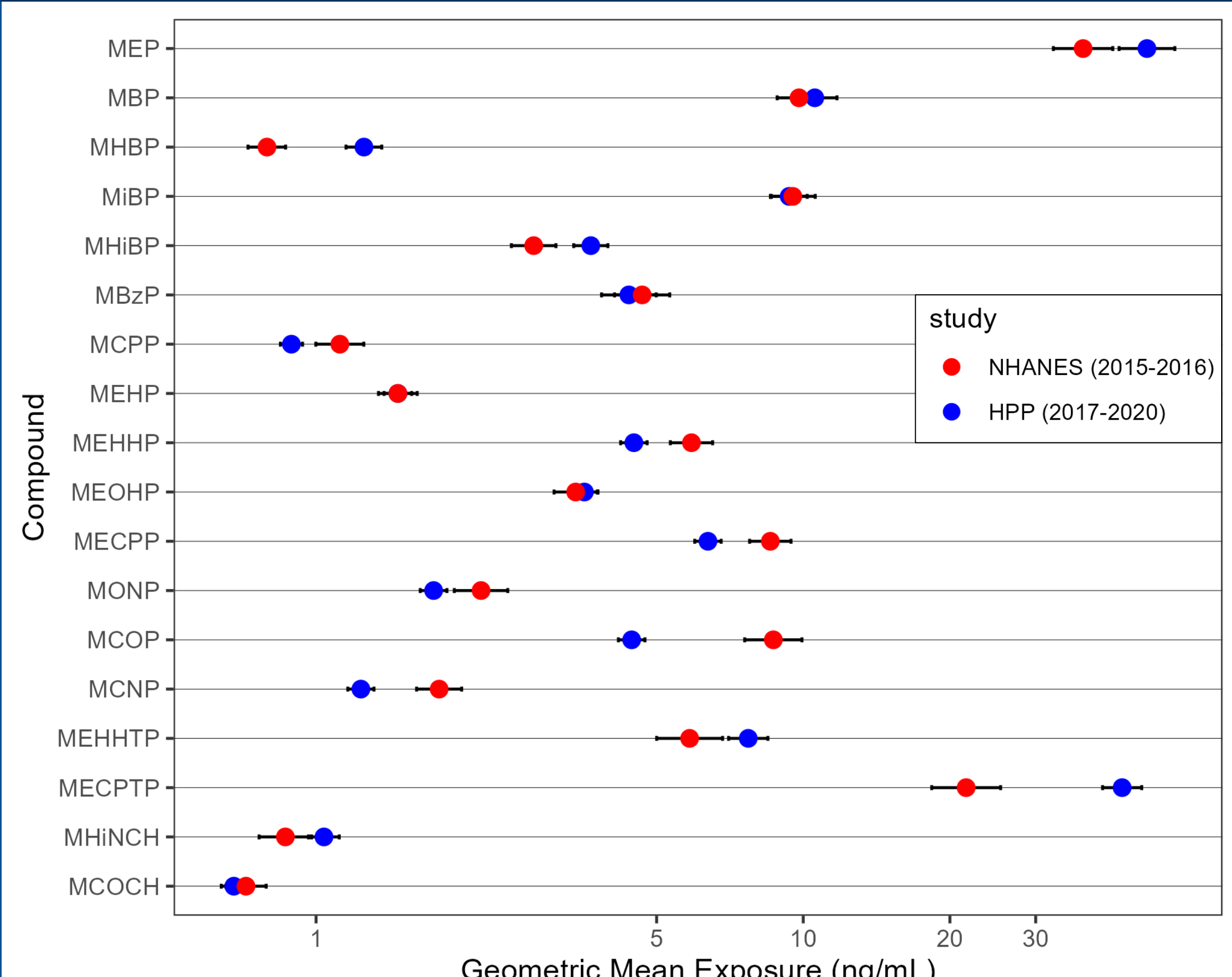
HPP vs. NHANES

Figure 3: Geometric mean exposure biomarker concentrations in the Human Placenta and Phthalates Study (HPP) compared to female-identifying participants of reproductive age within the 2015-2016 National Health and Nutrition Survey (NHANES).
HPP exposure biomarkers were measured by LC-MS and corrected for urine dilution using covariate-adjusted standardization plus specific gravity adjustment. Error bars represent 95% confidence interval.

Future Analyses in HPP

1. Investigate the association between phthalate exposure & hazard of developing PE considering time-to-diagnosis
2. Explore the association between average gestational phthalate and replacement exposure & blood pressure across pregnancy
3. Measure and assess urinary biomarkers of preeclampsia to elucidate mechanism(s) underlying these associations

Acknowledgments