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Exposure to Endocrine Disrupting Chemicals (EDCs) and Cardiometabolic Indices During Pregnancy: The HOME Study

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Exposure to endocrine disrupting chemicals (EDCs) and cardiometabolic indices during pregnancy: The HOME Study

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ABSTRACT

Background: Toxicology studies have identified pregnancy as a window of susceptibility for endocrine disrupting chemicals (EDCs) and cardiometabolic indices in women. No study in humans, however, has examined EDC mixtures and cardiometabolic indices during pregnancy. **Methods**: We used the Health Outcomes and Measures of the Environment (HOME) Study to examine whether bisphenol A (BPA), polybrominated diphenyl ethers (PBDEs), per- and polyfluoroalkyl substances (PFAS), and phthalates are associated with blood pressure, glucose, and lipids in 388 pregnant women. We measured PBDEs and PFAS in serum at 16 weeks gestation, while BPA and phthalate metabolites were quantified in urine at 16 and 26 weeks gestation. We used linear regression and Bayesian Kernel Machine Regression (BKMR) to estimate covariate-adjusted associations of individual EDCs and their mixtures with cardiometabolic indices during pregnancy. **Results**: A 10-fold increase in BDE-28 was associated with a 13.1 mg/dL increase in glucose (95% Confidence Interval [CI] 2.9, 23.2) in linear regression. The BKMR model also identified BDE-28 as having a positive association with glucose. BDE-28, BDE-47, and BDE-99 were positively associated with total cholesterol in both single- and multi-pollutant models, whereas a suggestive negative association was noted with BDE-153. Mono-n-butyl phthalate (MBP) (β = -7.9 mg/dL, 95% CI −12.9, −3.0) and monobenzyl phthalate (MBzP) ($\beta = -6.3$ mg/dL, 95% CI −10.6, −2.0) were both associated with significant decreases in cholesterol in linear regression, but only MBzP was identified as an important contributor in the BKMR model. **Conclusion**: Overall, we observed positive associations between PBDEs with glucose and cholesterol levels during pregnancy, while negative associations were found between some phthalate biomarkers and cholesterol. No relationship was noted for BPA or PFAS with cardiometabolic indices during pregnancy across both models.

1. Introduction

Pregnant women are routinely exposed to endocrine disrupting chemicals (EDCs), including bisphenol A (BPA), polybrominated diphenyl ethers (PBDEs), per- and polyfluoroalkyl substances (PFAS), and phthalates (Woodruff et al., 2011). Pregnancy is underappreciated as a potentially sensitive period of susceptibility for women's cardiometabolic health, because of the marked cellular proliferation and development, metabolic changes, and epigenetic programming that occurs. Research has predominantly focused on the offspring as the target of adverse effects resulting from EDC exposure during pregnancy (Ashley-Martin et al., 2014; Braun et al., 2014, 2016; de Cock et al., 2014; Erkin-Cakmak et al., 2015; Harley et al., 2013; Hoyer et al., 2015; Valvi et al., 2015; Volberg et al., 2013). However, animal studies

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provide evidence that EDCs' effects extend to the mother as well (Alonso-Magdalena et al., 2015; Alonso-Magdalena et al., 2010). Pregnant mice exposed to 10 μg/kg/d of BPA on gestational days 9–16 (GD9-16) had higher weight, plasma triglyceride levels, and fasting plasma insulin on GD18 than their non-BPA treated counterparts (Alonso-Magdalena et al., 2010). Pregnant mice dosed with 100 μg/kg/d of BPA had increased insulin resistance as well as glucose intolerance, and significantly higher fasting plasma insulin, triglycerides, glycerol, and leptin levels relative to controls on GD18.

Some epidemiological studies have found significant associations between EDC exposures during pregnancy and gestational diabetes, pregnancy-induced hypertensive disorders, and changes in glucose levels and lipid profiles during pregnancy (Fisher et al., 2018; Huang et al., 2019; James-Todd et al., 2018; Jensen et al., 2018; Matilla-Santander et al., 2017; Rahman et al., 2019; Starling et al., 2014; Shaffer et al., 2019; Werner et al., 2015; Zhang et al., 2015). PFAS compounds, including perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA), have been positively associated with gestational diabetes in prospective cohorts in Denmark, Spain, and in the United States (Jensen et al., 2018; Matilla-Santander et al., 2017; Rahman et al., 2019; Zhang et al., 2015). First trimester concentrations of mono-iso-butyl phthalate (MiBP) and monoethyl phthalate (MEP) were also positively associated with gestational diabetes in the Cambridge Baby Growth Study and The Infant Development and Environment Study (TIDES), respectively; the TIDES also noted similar associations with third trimester MEP (Fisher et al., 2018; Shaffer et al., 2019). However, among 245 subfertile women, higher concentrations of MEP during the second trimester of pregnancy were associated with elevated glucose levels, while there were inverse associations with MiBP (James-Todd et al., 2018). With regard to changes in blood pressure during pregnancy, increased concentrations of monobenzyl phthalate (MBzP) were associated higher diastolic blood pressure during pregnancy and increased risk of pregnancy-induced hypertension diseases (Werner et al., 2015). A number of PFAS compounds were also associated with increased risk of preeclampsia and hypertensive disorders during pregnancy in a cross-sectional study in China (Huang et al., 2019). Additionally, PFAS measured at 17–20 weeks gestation were positively associated with total cholesterol and high-density lipoprotein (HDL) levels in a cross-sectional analysis of women in the Norwegian Mother and Child (MoBa) Cohort Study (Starling et al., 2014). While the Spanish INMA (Environment and Childhood Project [INfancia y Medio Ambiente]) birth cohort study also noted higher first trimester total cholesterol with increased PFOA concentrations, PFOS and PFNA were inversely associated with triglycerides (Matilla-Santander et al., 2017).

Although some epidemiological studies have examined individual classes of environmental contaminants during pregnancy and cardiometabolic indices, no study has examined mixtures of EDCs in relation to cardiometabolic indices in pregnant women. Using the Health Outcomes and Measures of the Environment (HOME) Study, we examined whether maternal exposure to EDCs, including BPA, PBDEs, PFAS, and phthalates, are associated with cardiometabolic profiles of women during pregnancy using both single-pollutant and multi-pollutant mixture approaches.

2. Methods

2.1. Study participants and design

We used data from the HOME Study, an ongoing prospective pregnancy and birth cohort, for the present study. Cohort details have been previously published (Braun et al., 2020; Braun et al., 2017). Briefly, pregnant women who were at least 18 years of age were recruited from nine prenatal clinics in the Greater Cincinnati Area (Ohio, US) between March 2003 and February 2006. To enroll in the study, women had to meet the following inclusion criteria: 1) 16 ± 3 weeks of gestation; 2) residing in housing constructed before 1978; 3) receiving and planning to continue prenatal care and deliver at one of the collaborating obstetric practices; 4) HIV negative status; and 5) not taking any medications related to seizures, thyroid disorders, or chemotherapy/radiation. A total of 468 women were enrolled, and 388 remained in the study to deliver liveborn singletons without congenital anomalies. For the current analysis, 388 HOME Study women were included since they had measurements of at least one EDC biomarker at either 16 or 26 weeks gestation (BPA, PBDEs, PFAS, phthalates) and at least one cardiometabolic outcome measure during pregnancy (blood pressure, lipids, glucose). This study was approved by the institutional review board (IRB) at the Cincinnati Children's Hospital Medical Center (CCHMC); the Centers for Disease Control and Prevention (CDC) and collaborating institutions relied on CCHMC's IRB as the IRB of record.

2.2. Assessment of EDCs

Serum was separated from blood samples that were obtained at 16 ± 3 weeks of gestation via venipuncture and subsequently stored at −80 °C until quantification. Gas chromatography/isotope dilution high-resolution mass spectrometry and high-performance liquid chromatography-isotope dilution-tandem mass spectrometry were used to quantify serum PBDEs and PFAS, respectively (Jones et al., 2012; Kato et al., 2011; Sjodin et al., 2004). For PBDEs, each batch included 3 quality control and 3 method blanks. For PFAS, calibration standards were spiked into calf serum to account for potential matrix effects and each analytical batch included reagent blanks and low- and high-concentration quality control materials (Kato et al., 2014). Mean and standard deviation (SD) recovery rates for PBDE congeners ranged from 77 ± 8% to 84 ± 12%. For PFAS, the recovery rates ranged between 72 ± 4% and 109 ± 8%. Lipid standardization was conducted for PBDEs to account for PBDEs' lipophilic nature (Phillips et al., 1989). However, we analyzed PBDE concentrations as pg/g serum, because our outcomes were either lipid-related or were measurements of lipid levels. Most women had serum at 16 weeks gestation for PFAS measurements. We used serum samples at 26 weeks (n = 35) or at delivery (n = 17) for women who did not have serum sample measurements at 16 weeks. If more than one PFAS measurement was available during pregnancy (n = 70), an average was used. Concentrations of PFAS are expressed as ng/mL.

Two spot urine samples were collected at approximately 16 and 26 weeks using polypropylene specimen cups not known to contain detectable levels of BPA or phthalates. Urine was stored at or below −20 °C until analysis for BPA and phthalate metabolites. BPA was measured using online solid phase extraction coupled to high performance liquid chromatography-isotope dilution tandem mass spectrometry (Ye et al., 2005). Each analytical run included four quality control samples. The recovery rate for BPA was 88%. Phthalate metabolites, including MEP, mono-n-butyl phthalate (MBP), MiBP, MBzP, mono (3-carboxypropyl) phthalate (MCPP), mono (2-ethyl-5-carboxypentyl) phthalate (MECPP), mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono (2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono (2-ethylhexyl) phthalate (MEHP), were measured using procedures described elsewhere (Silva et al., 2008) Each analytical run included two low- and two high-concentration quality control samples. Recovery rates for phthalate biomarkers ranged from 93 ± 3% to 109 ± 1%. A summary measure of the di(2-ethylhexyl) phthalate (DEHP) metabolites (∑DEHP) was calculated by taking the molar sum of the urinary concentrations of each DEHP metabolite (MECPP, MEHP, MEHHP, and MEOHP). To account for urine dilution, BPA (ng/mL) and phthalate metabolites (ng/mL) were creatinine-standardized and are expressed as μg/g creatinine. Creatinine standardized BPA (μg/g creatinine) was calculated by

dividing the volume-based measure (ng/mL) by urinary creatinine (mg/dL) and multiplying by 100. We expressed ΣDEHP as μg/g creatinine by multiplying the molar sum (μmol/g creatinine) of MEHP, MEHHP, MEOHP, and MECPP by the molecular weight of MECPP (308 g/mol). BPA and phthalates at 16 weeks and 26 weeks were analyzed separately, depending on the cardiometabolic outcome and its timing.

The limit of detection (LOD) for BPA, PBDEs, PFAS, and phthalates were 0.4 ng/mL, 0.2–8.2 ng/g lipid, 0.1–0.2 ng/mL, and 0.2–1.2 ng/mL, respectively. Concentrations below the LOD were replaced with LOD/$\sqrt{2}$ (Hornung and Reed, 1990). To reduce the influence of outliers, PBDEs were $\log_{10}$-transformed due to a wider range of concentrations, while BPA, PFAS, and phthalates were ln-transformed since these EDCs have a narrower range of concentrations. For the present study, we included the following EDCs: 1) BPA at 16 and 26 weeks; 2) PBDEs (BDE-28, −47, −99, −100, and −153); 3) PFAS (PFOS, PFOA, PFHxS, and PFNA); and 4) phthalate metabolites at 16 and 26 weeks (MEP, MBP, MiBP, MBzP, MCPP, and ∑DEHP).

2.3. Cardiometabolic indices during pregnancy

We performed a medical chart review of HOME Study participants to obtain information on anthropometrics, blood pressure, and glucose. For systolic and diastolic pressure, we used the highest blood pressure reading after 20 weeks gestation (n = 383). The average gestational week of the blood pressure measurement was 30.6 ± 5.6 weeks. Non-fasting glucose levels were measured in blood samples collected at 1-hour after drinking 50 g glucose load at ≥ 26 weeks gestation (n = 234), with the average assessment completed at approximately 27.6 ± 1.4 weeks gestation. Non-fasting lipid measures (n = 368), including total lipids, cholesterol, and triglycerides, were quantified at 16 weeks gestation using standard enzymatic, colorimetric methods (Phillips et al., 1989). We assume that cholesterol ester accounts for 73% of total cholesterol and that phospholipids have a linear relationship with total cholesterol (Bernert et al., 2007). We did not take into account the variations in cholesterol esterase during pregnancy as little is known regarding esterase activity in pregnant women. We do not have information regarding a diagnosis of hypertension prior to pregnancy. However, HOME Study women provided information on their usage of antihypertensive medications. Among the 388 included participants, a total of 21 indicated usage of medications for high blood pressure. We created a composite measure for pregnancy-induced hypertensive disorders using chart-derived diagnoses of either gestational hypertension (n = 20), preeclampsia (n = 23), or eclampsia (n = 0). Women who met one of the following criteria after 20 weeks gestation were also considered to have a pregnancy-induced hypertensive disorder: 1) two systolic blood pressure measurements > 140 mmHg; 2) two diastolic blood pressure measurements > 90 mmHg; or 3) one systolic blood pressure measurement > 140 mmHg and one diastolic blood pressure measurement > 90 mmHg.

2.4. Statistical methods

We used separate multiple linear regression models to estimate β coefficients and 95% confidence intervals (CIs) for individual EDCs in relation to each cardiometabolic index. Final models were adjusted for covariates identified based on a literature review and bivariate analyses (p < 0.20) and included: age, race/ethnicity (non-Hispanic Whites, non-Hispanic Blacks and Others [Hispanics, Asians/Pacific Islanders, and Native Americans comprised of only 6.7% of the 388 included participants]), annual household income, smoking status based on serum cotinine levels quantified at 16 weeks gestation (<1 ng/mL; 1–9 ng/mL; ≥10 ng/mL), marijuana use via self-report, serum concentrations of ∑PCBs (polychlorinated biphenyls), prepregnancy body mass index [BMI] (underweight/normal, <25.0 kg/m^3; overweight, 25.0–29.9 kg/m^3; obese, ≥30 kg/m^3), and parity. We additionally adjusted for gestational week in all analyses for blood pressure. We also used Bayesian Kernel Machine Regression (BKMR), a nonparametric high-dimensional exposure–response function using kernel machine regression with component-wise or hierarchical variable selection with 10,000 iterations, to account for complex EDC mixtures and to identify joint interactions (Bobb et al., 2015). Each EDC within the model is assigned a posterior inclusion probability (PIP). BKMR models additionally generate dose response patterns for each EDC component within the model itself. We used R package "bkmr" to construct these multi-pollutant models for each cardiometabolic outcome measure. For a secondary analysis, we estimated relative risks (RRs) and 95% CIs using Poisson regression with robust error variances for associations between EDCs at 16 weeks and pregnancy-induced hypertensive disorders (Zou, 2004). We additionally examined for potential interactions between two EDC compounds when all other chemicals are held at median levels in reduced BKMR models that contained chemicals with the highest PIPs, indicating the greatest contribution to the association. We focused on positive or negative associations that were consistently observed between single- and multi-pollutant models.

We estimated associations between PBDEs, PFAS, as well as BPA and phthalate metabolites quantified at 16 weeks with every cardiometabolic index. For BPA and phthalate metabolites quantified at 26 weeks, we analyzed their associations with glucose measured ≥ 26 weeks gestation. In a sensitivity analysis, we examined all associations using PFAS measured only at 16 ± 3 weeks gestation, instead of the averaged PFAS concentrations during pregnancy. We additionally analyzed PBDEs with lipid adjustment (ng/g lipid) in the analysis of glucose. We also adjusted for intake of fruits and vegetables during pregnancy (at least once a day, less than daily), which was obtained using a self-reported questionnaire, and removed prepregnancy BMI from the models. Lastly, we performed three sensitivity analyses with regard to antihypertensive medication usage, including: 1) adjustment for antihypertensive medication usage; 2) taking into account treatment effects of antihypertensive drug usage by adding 10 mmHg and 5 mmHg to systolic and diastolic blood pressure measurements, respectively (Balakrishnan et al., 2017; Tobin et al., 2005); and 3) removing women using antihypertensive medications from the analysis. Goodness of fit was checked using residual plots and the Breusch-Pagan test for heteroskedasticity. Due to the small sample size, we did not split the dataset to obtain training and validation datasets. Stata version 16.0 and R version 3.6.1 were used for statistical analyses.

3. Results

3.1. Study participants

A total of 388 HOME Study women were included in the analysis. The majority of women were non-Hispanic white (61.8%), between the ages of 25–34 years (59.4%), and had some college education or higher (73.8%). Most women were either married or living with a partner (79.3%), had a serum cotinine level < 1 ng/mL (82.7%), and had a BMI ≥ 25 kg/m^2 (57.4%). The geometric mean (GM) was highest for: PFOS (12.7 ± 1.7 ng/mL) within the PFAS, BDE-47 (20.7 ± 2.6 ng/g lipid) within PBDEs, and MEP (134.4 ± 4.0 ng/mL and 111.3 ± 4.8 ng/mL) within phthalate biomarkers measured at 16 and 26 weeks gestation (Supplemental Table S1). Overall, concentrations of phthalate biomarkers were higher at 16 weeks gestation compared to 26 weeks gestation. Similar decreases across pregnancy have been found in previous epidemiological studies and is likely influenced by potential behavioral changes as pregnancy progresses, specifically women opting to consume fresh foods and those foods with less packaging (Braun et al., 2012; Ferguson et al., 2014; Rudel et al., 2011). BPA concentrations were similar between 16 and 26 weeks gestation. Characteristics that

Table 1
Cardiometabolic indices during pregnancy by sociodemographics, behavioral, and obstetric characteristics, HOME Study.[a]

	Systolic blood pressure		Diastolic blood pressure		Total lipids	Total cholesterol	Triglycerides	Glucose	
	n	Mean ± SD	Mean ± SD	n	Mean ± SD	Mean ± SD	Mean ± SD	n	Mean ± SD
Age, years									
<25	93	117.6 ± 15.1	71.9 ± 9.0	89	607.3 ± 98.4*	183.6 ± 34.6*	128.2 ± 42.8*	52	95.0 ± 27.2*
25–34	229	117.9 ± 14.0	72.0 ± 9.3	221	668.0 ± 116.4*	203.3 ± 38.0*	144.3 ± 50.3*	144	105.1 ± 25.4*
≥35	61	116.1 ± 10.3	71.4 ± 7.9	57	679.3 ± 105.0*	205.9 ± 34.7*	149.6 ± 51.8*	38	106.5 ± 26.5*
Race/ethnicity									
Non-Hispanic White	236	116.6 ± 13.4	71.3 ± 8.6	224	664.5 ± 117.1*	200.8 ± 38.0	146.4 ± 51.7*	149	107.2 ± 26.4*
Non-Hispanic Black and Others	143	118.4 ± 12.8	72.6 ± 9.5	138	641.1 ± 108.2*	196.0 ± 37.6	133.9 ± 44.7*	83	96.3 ± 24.6*
Education									
High school or less	98	118.9 ± 12.4	72.6 ± 9.4	95	631.4 ± 113.1*	191.1 ± 39.7*	135.1 ± 45.9	61	98.0 ± 23.7
Some college/2 yr degree	90	115.4 ± 11.8	71.0 ± 8.1	83	637.9 ± 106.3*	193.3 ± 36.6*	136.8 ± 45.0	50	104.2 ± 29.0
Bachelor's	110	116.7 ± 13.9	71.4 ± 9.4	108	669.9 ± 109.0*	202.8 ± 34.6*	147.3 ± 56.4	69	105.0 ± 26.6
Graduate or professional	81	118.2 ± 14.4	72.0 ± 8.8	76	684.9 ± 123.3*	209.4 ± 38.7*	147.2 ± 47.2	52	106.2 ± 25.8
Family Income									
<$40,000	148	117.2 ± 12.2	71.5 ± 8.8*	141	633.1 ± 112.0*	192.4 ± 38.7*	134.0 ± 45.5*	85	99.6 ± 24.9*
$40,000-$79,999	128	118.3 ± 14.9	73.2 ± 9.4*	121	662.3 ± 112.3*	198.2 ± 34.9*	150.0 ± 52.1*	85	108.8 ± 27.9*
≥$80,000	103	116.2 ± 12.4	70.3 ± 8.3*	100	679.3 ± 114.8*	209.0 ± 38.2*	142.5 ± 50.5*	62	100.9 ± 24.8*
Depressive symptoms									
Minimal/mild	346	117.3 ± 13.2	71.7 ± 9.0	330	656.7 ± 114.4	199.0 ± 37.2	142.6 ± 50.3	213	103.3 ± 25.4
Moderate/severe	30	116.8 ± 12.8	71.3 ± 8.5	30	648.9 ± 114.6	198.7 ± 45.5	135.5 ± 38.9	18	101.3 ± 34.6
Alcohol Consumption									
Never	214	117.4 ± 12.1	72.8 ± 8.4*	205	646.2 ± 114.4	195.3 ± 37.5	140.6 ± 48.4	131	102.7 ± 27.3
<1 per month	114	117.7 ± 15.3	70.5 ± 9.8*	110	663.6 ± 115.6	201.9 ± 37.6	143.1 ± 51.1	69	104.3 ± 23.8
≥1 per month	51	115.8 ± 12.8	70.4 ± 8.8*	47	677.7 ± 107.7	208.1 ± 38.8	142.9 ± 51.3	32	103.5 ± 27.7
Marijuana Use									
No	351	117.4 ± 13.1	71.9 ± 8.9	335	656.0 ± 111.0	199.1 ± 36.4	141.7 ± 48.5	215	102.8 ± 26.4
Yes	28	115.3 ± 14.2	70.1 ± 9.9	27	650.4 ± 150.5	196.7 ± 53.5	141.5 ± 61.4	17	109.1 ± 24.3
Serum cotinine (ng/mL)									
<1	318	117.4 ± 13.3	71.7 ± 9.1	305	657.9 ± 110.0	199.9 ± 35.9	141.8 ± 49.2	196	103.3 ± 26.6
1–9	34	116.1 ± 12.3	72.0 ± 8.0	32	647.2 ± 131.7	195.5 ± 41.4	141.3 ± 57.6	18	100.9 ± 24.5
≥10	31	120.8 ± 19.1	73.6 ± 9.3	30	635.2 ± 130.4	192.8 ± 49.8	135.3 ± 41.2	20	102.7 ± 25.4
Vitamin Use									
Daily	291	117.7 ± 13.6	72.2 ± 9.1	279	658.3 ± 114.9	199.1 ± 37.4	144.2 ± 49.9	180	103.9 ± 26.9
<Daily	61	114.7 ± 11.6	70.7 ± 8.2	58	651.4 ± 121.4	200.2 ± 42.7	134.7 ± 50.6	36	102.7 ± 24.9
Never	27	118.3 ± 12.4	69.5 ± 8.8	25	633.8 ± 87.8	194.4 ± 31.5	130.2 ± 39.9	16	97.4 ± 22.0
Fruit and Vegetable Intake									
Daily	301	117.5 ± 13.6	71.6 ± 9.0	287	658.6 ± 113.4	199.7 ± 36.7	143.0 ± 51.7	194	103.7 ± 25.6
<Daily	78	116.4 ± 11.6	72.4 ± 8.9	75	644.1 ± 117.1	196.1 ± 42.0	136.6 ± 39.9	38	101.1 ± 29.7
Prepregnancy BMI									
Underweight/Normal	164	114.7 ± 13.1*	69.6 ± 8.3*	155	641.0 ± 101.8	197.4 ± 33.9	130.5 ± 44.2*	101	97.5 ± 25.4*
Overweight	125	117.5 ± 14.3*	72.2 ± 9.7*	121	668.1 ± 125.9	201.6 ± 41.2	148.2 ± 56.0*	83	106.4 ± 26.8*
Obese	94	122.5 ± 12.9*	75.4 ± 8.1*	91	661.8 ± 114.0	197.8 ± 38.9	150.3 ± 45.0*	50	108.9 ± 25.2*
Parity									
Nulliparous	170	118.8 ± 15.6	72.2 ± 9.5	162	652.5 ± 115.1	198.6 ± 37.3	139.3 ± 52.1	105	102.8 ± 24.4
Primiparous	120	115.6 ± 12.6	70.7 ± 8.4	112	644.7 ± 114.7	194.7 ± 37.5	140.5 ± 47.9	72	103.3 ± 28.8
Multiparous	91	117.7 ± 11.4	73.1 ± 8.5	91	672.9 ± 109.4	204.5 ± 38.4	146.4 ± 46.1	57	103.3 ± 26.6
Marital status									
Married/living with partner	302	117.5 ± 13.8	71.9 ± 9.0	287	660.1 ± 114.7	200.1 ± 37.2	143.6 ± 50.3	184	105.5 ± 26.7
Not married, living alone	77	116.4 ± 10.6	71.2 ± 8.7	75	638.2 ± 111.4	194.5 ± 40.1	134.4 ± 45.6	48	94.7 ± 22.6

Units: Systolic and diastolic blood pressure (mmHg); glucose, total lipids, total cholesterol, and triglycerides (mg/dL).
[a] Frequencies may not add to the total number of participants because of missing values. * $p < 0.05$ (two-sided p-values using analysis of variance).

were significantly predictive of higher concentrations of PFOA and PFOS included being non-Hispanic white, having an income ≥$80,000 (PFOS only), and being nulliparous (Supplemental Table S2). Concentrations of BDE-47 were significantly higher for women < 25 years of age and among those who self-identified as non-Hispanic black or other. We also observed higher BDE-47 concentrations among women with less than an undergraduate degree, those with a lower family income, and those who were not married or living alone. BDE-47 concentrations were significantly lower among women who were not obese as well as among women who took vitamin supplementation during pregnancy and who did not use tobacco or marijuana. For ∑DEHP at 16 and 26 weeks, higher concentrations were observed among women with higher educational attainment.

The mean systolic and diastolic blood pressure were 117.6 ± 13.8 and 71.9 ± 9.0 mmHg, respectively. For lipids, cholesterol, and triglycerides, mean levels were 655.2 ± 113.5, 199.0 ± 37.6, and 141.2 ± 49.3 mg/dL, respectively. Mean glucose levels measured at ≥ 26 weeks gestation was 103.1 ± 26.2 mg/dL. Having a prepregnancy BMI considered as obese was significantly associated with increased blood pressure (Table 1). Higher lipid levels were observed among older women and among women who identified as non-Hispanic white. Women with higher educational attainment and those with higher family income additionally had higher lipid levels. Lastly, we observed increased glucose levels among women who were older, non-Hispanic white, and those who were obese prior to pregnancy.

3.2. Single-pollutant analyses

Overall we found no significant associations between concentrations of BPA at 16 weeks gestation or PBDEs with systolic or diastolic blood pressure (Table 2). However, a significant increase in diastolic blood pressure was observed with higher concentrations of PFOS. In addition, a ln-unit increase in MEP at 16 weeks gestation was significantly associated with a 1.2 mmHg (95% CI 0.04, 2.4) and 0.8 mmHg (95% CI 0.02,

Table 2
Change in blood pressure measures during pregnancy per ln-unit or 10-fold increase in EDC concentrations, HOME Study.[a]

	Systolic blood pressure β (95% CI)	Diastolic blood pressure β (95% CI)
BPA[b, c]	-0.05 (-1.7, 1.6)	0.3 (-0.8, 1.3)
PBDEs[d]		
BDE-28	−0.5 (−4.4, 3.4)	1.8 (−0.6, 4.3)
BDE-47	0.6 (−2.9, 4.0)	1.7 (−0.5, 3.9)
BDE-99	0.5 (−2.8, 3.8)	1.8 (−0.3, 3.9)
BDE-100	0.7 (−2.5, 4.0)	1.4 (−0.7, 3.4)
BDE-153	1.6 (−1.6, 4.7)	0.6 (−1.4, 2.6)
PFAS[b]		
PFOA	−1.1 (−3.8, 1.5)	−0.3 (−2.0, 1.4)
PFOS	−0.03 (−2.7, 2.6)	1.9 (0.2, 3.6)
PFNA	0.5 (−3.0, 4.1)	1.5 (−0.8, 3.8)
PFHxS	−0.3 (−2.2, 1.6)	1.1 (−0.1, 2.3)
Phthalate biomarkers[b, c]		
MBP	0.4 (−1.3, 2.1)	0.3 (−0.8, 1.4)
MBzP	1.1 (−0.4, 2.6)	0.9 (−0.1, 1.8)
MCPP	2.1 (0.2, 4.1)	−0.1 (−1.3, 1.2)
MEP	1.2 (0.04, 2.4)	0.8 (0.02, 1.5)
MiBP	−1.0 (−2.8, 0.8)	0.1 (−1.1, 1.2)
∑DEHP	0.3 (−1.0, 1.6)	−0.5 (−1.3, 0.3)

Units: BPA and phthalates, μg/g creatinine; PBDEs, pg/g; PFAS, ng/mL; systolic and diastolic blood pressure, mmHg.
∑DEHP = MECPP, MEHP, MEHHP, and MEOHP.
[a] Adjusted by age, race/ethnicity, household income, smoking status, marijuana use, serum ∑PCBs, prepregnancy BMI, parity, and gestational week.
[b] Per ln-unit increase; [c] 16 weeks of gestation; [d] Per 10-fold increase

Table 3
Change in lipid measure and glucose during pregnancy per ln-unit or 10-fold increase in EDC concentrations, HOME Study.[a]

	Lipids β (95% CI)	Cholesterol β (95% CI)	Triglycerides β (95% CI)	Glucose β (95% CI)
BPA[b]				
16 weeks	−5.0 (−20.2, 10.1)	−2.1 (−7.1, 2.9)	−0.2 (−6.8, 6.4)	−2.6 (−7.4, 2.2)
26 weeks	–	–	–	−0.1 (−4.2, 4.0)
PBDEs[c]				
BDE-28	34.2 (−1.0, 69.4)	13.2 (1.7, 24.8)	4.2 (−11.3, 19.6)	13.1 (2.9, 23.2)
BDE-47	28.1 (−3.3, 59.6)	11.5 (1.2, 21.8)	2.0 (−11.8, 15.8)	8.9 (−0.2, 17.9)
BDE-99	26.8 (−3.5, 57.1)	10.9 (1.0, 20.8)	2.0 (−11.2, 15.3)	5.1 (−3.7, 13.8)
BDE-100	18.1 (−11.5, 47.7)	7.3 (−2.4, 17.1)	1.4 (−11.5, 14.4)	8.4 (−0.1, 16.9)
BDE-153	−1.1 (−29.8, 27.7)	0.7 (−8.7, 10.2)	−2.8 (−15.3, 9.8)	6.6 (−1.6, 14.7)
PFAS[b]				
PFOA	−0.2 (−5.1, 24.8)	−1.3 (−9.6, 7.0)	2.8 (−8.2, 13.7)	1.7 (−5.6, 8.9)
PFOS	−11.3 (−36.5, 13.9)	−4.3 (−12.6, 4.1)	−1.6 (−12.8, 9.5)	−1.1 (−9.0, 6.7)
PFNA	−0.9 (−34.6, 32.9)	−2.0 (−13.3, 9.2)	3.6 (−11.1, 18.7)	6.9 (−3.8, 17.6)
PFHxS	−5.3 (−23.5, 12.9)	−4.0 (−10.1, 2.0)	3.8 (−4.2, 11.8)	−2.1 (−7.5, 3.3)
Phthalate biomarkers[b]				
16 weeks				
MBP	−21.0 (−36.1, −5.9)	−7.9 (−12.9, −3.0)	−2.9 (−9.6, 3.7)	2.8 (−1.7, 7.4)
MBzP	−18.7 (−31.9, −5.6)	−6.3 (−10.6, −2.0)	−4.4 (−10.2, 1.3)	−0.5 (−4.9, 3.8)
MCPP	−18.7 (−36.0, −1.3)	−4.7 (−10.4, 1.0)	−8.0 (−15.5, −0.4)	−2.3 (−8.2, 3.7)
MEP	−1.1 (−11.9, 9.7)	−0.1 (−3.7, 3.5)	−0.8 (−5.5, 3.9)	−0.2 (−3.4, 3.1)
MiBP	−10.9 (−27.1, 5.3)	−2.0 (−7.3, 3.4)	−6.4 (−13.4, 0.7)	1.3 (−3.4, 6.0)
∑DEHP	−3.6 (−15.1, 7.9)	−0.8 (−4.5, 3.0)	−1.9 (−6.8, 3.1)	−1.0 (−4.5, 2.5)
26 weeks				
MBP	–	–	–	0.4 (−4.3, 5.1)
MBzP	–	–	–	−3.4 (−7.6, 0.7)
MCPP	–	–	–	−2.0 (−7.4, 3.5)
MEP	–	–	–	−1.5 (−4.3, 1.4)
MiBP	–	–	–	−2.3 (−6.6, 1.9)
∑DEHP	–	–	–	0.3 (−3.2, 3.9)

Units: BPA and phthalates, μg/g creatinine; cholesterol, glucose, lipids, and triglycerides, mg/dL; PBDEs, pg/g; PFAS, ng/mL.
∑DEHP = MECPP, MEHP, MEHHP, and MEOHP.
[a] Adjusted by age, race/ethnicity, household income, smoking status, marijuana use, serum ∑PCBs, prepregnancy BMI, and parity.
[b] Per ln-unit increase; [c] Per 10-fold increase.

1.5) increase in systolic and diastolic blood pressure, respectively. MCPP at 16 weeks was positively associated with systolic blood pressure (β = 2.1 mmHg, 95% CI 0.2, 4.1). No relationship was noted between any EDC compound and pregnancy-induced hypertensive disorders (Supplemental Table S3). We found a significant positive association between BDE-28 with glucose (Table 3). Specifically, a 10-fold increase in BDE-28 was associated with a 13.1 mg/dL (95% CI 2.9, 23.2) increase in serum glucose concentration. No relationship was noted between BPA (16 or 26 weeks), PFAS, or phthalate biomarkers (16 or 26 weeks) with glucose levels.

We observed significant negative associations between MBP, MBzP, and MCPP at 16 weeks with total lipids (Table 3). In addition, a ln-unit increase in MBP and MBzP was associated with a decrease of 7.9 mg/dL (95% CI −12.9, −3.0) and 6.3 mg/dL (95% CI −10.6, −2.0) in total cholesterol, respectively. For triglycerides, there was an inverse association with MCPP (β = -8.0 mg/dL, 95% CI −15.5, −0.4). In contrast, statistically significant positive associations were observed with several PBDE congeners. Ten-fold increases in BDE-28, BDE-47, and BDE-99 were associated with an increase of 13.2 mg/dL (95% CI 1.7, 24.8), 11.5 mg/dL (95% CI 1.2, 21.8), and 10.9 mg/dL (95% CI 1.0, 20.8) in total cholesterol, respectively. No associations were observed between individual DEHP metabolites MECPP, MEHP, MEHHP, or MEOHP with any of the cardiometabolic indices during pregnancy (Supplemental Table S4).

3.3. Multi-pollutant analyses

No EDC was identified as an important contributor in the BKMR analysis with component-wise variable selection for systolic and diastolic blood pressure (Supplemental Table S5). In the analysis with glucose, only BDE-28 was found to be an important contributor to the positive association (PIP > 0.5) in the analyses of EDC mixtures at 16 weeks gestation (Table 4; Supplemental Fig. S1). When we examined mixtures of EDCs at 26 weeks gestation, MBzP and BDE-28 were associated with glucose. However, increasing concentrations of MBzP at 26 weeks were associated with lower glucose levels, whereas BDE-28 was associated with higher glucose levels (Fig. 1). In the examination for potential interaction between six EDCs (PFOS, PFHxS, BDE-28, BDE-47, BDE-99, and MBzP at 26 weeks gestation) in the association with glucose, we did not observe synergistic or multiplicative interaction (Supplemental Fig. S2). All associations between each EDC with glucose remained mainly parallel despite the increase in the second EDC biomarker.

For total lipids, the BKMR analysis yield similar results as the linear regression models. PIPs were 0.38 and 0.25 for BDE-28 and BDE-47,

Table 4
Bayesian Kernel Machine Regression (BKMR) component-wise variable selection results for EDC concentrations and lipid measures and glucose during pregnancy.

EDC	Lipids PIP	Cholesterol PIP	Triglycerides PIP	Glucose PIP	Glucose PIP[d]
BPA[b]					
16 weeks	0.0248	0.0010	0.0604	0.1118	–
26 weeks	–	–	–	–	0.0204
PBDEs[c]					
BDE-28	0.3840	0.3826	0.0900	0.5034	0.5918
BDE-47	0.2452	0.3840	0.0658	0.1774	0.1816
BDE-99	0.1800	0.2174	0.0566	0.1614	0.1036
BDE-100	0.1036	0.2244	0.1082	0.1676	0.0716
BDE-153	0.1284	0.2228	0.0296	0.0468	0.0596
PFAS[b]					
PFOA	0.0152	0.0198	0.0446	0.0636	0.0392
PFOS	0.0000	0.0056	0.0134	0.1104	0.1556
PFNA	0.0210	0.0180	0.0762	0.1436	0.0876
PFHxS	0.0008	0.0060	0.0016	0.1754	0.0990
Phthalate biomarkers[b]					
16 weeks					
MBP	0.0776	0.2538	0.0116	0.0440	–
MBzP	0.1274	0.0206	0.5644	0.0416	–
MCPP	0.0478	0.0178	0.1638	0.0618	–
MEP	0.0000	0.0000	0.0060	0.0506	–
MiBP	0.0208	0.0196	0.0448	0.0856	–
∑DEHP	0.0056	0.0000	0.1832	0.0316	–
26 weeks					
MBP	–	–	–	–	0.0374
MBzP	–	–	–	–	0.3066
MCPP	–	–	–	–	0.0390
MEP	–	–	–	–	0.0506
MiBP	–	–	–	–	0.0464
∑DEHP	–	–	–	–	0.0548

Abbreviations: PIP, Posterior Inclusion Probabilities.
∑DEHP = MECPP, MEHP, MEHHP, and MEOHP.
Units: BPA and phthalates, μg/g creatinine; cholesterol, glucose, lipids, and triglycerides, mg/dL; PBDEs, pg/g; PFAS, ng/mL.
[a]Adjusted by age, race/ethnicity, household income, smoking status, marijuana use, serum ∑PCBs, prepregnancy BMI, and parity.
[b]Per ln-unit increase.
[c]Per 10-fold increase.
[d]PIPs for BKMR model with BPA and phthalates measured at 26 weeks.

respectively, with positive associations (Table 4; Fig. 2). High PIPs were consistently observed with several PBDEs in the analysis with cholesterol, indicating that PBDEs are important contributors in the relationship (Table 4). However, dose response patterns illustrate that there were positive associations between BDE-28, BDE-47, and BDE-99 with total cholesterol, while BDE-100 and BDE-153 had negative associations (Fig. 3). No evidence of synergistic or multiplicative interaction was observed in the reduced BKMR model between the six EDCs, including BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, and MBP at 16 weeks, with total cholesterol (Supplemental Fig. S3). While PBDEs were identified as important and borderline contributors in the EDC mixture for associations with total lipids and cholesterol, only MBzP at 16 weeks had a high PIP (>0.30) with triglycerides. In particular, there was a U-shaped dose response relationship between MBzP and triglycerides (Fig. 4).

3.4. Sensitivity analyses

Final conclusions did not differ when we examined PFAS measured only at 16 weeks gestation, though we did note a positive association between PFOS at 16 weeks with diastolic blood pressure (Supplemental Table S6). No differences were observed when we analyzed PBDEs after lipid normalization in the relationship with glucose (Supplemental Table S7). Overall, results were similar after we adjusted for fruit and vegetable intake during pregnancy (Supplemental Tables S8 and S9). Once we removed prepregnancy BMI from the models, however, we also observed borderline significant positive associations with diastolic blood pressure for a number of EDCs, including BDE-28, BDE-47, BDE-99, and PFOS (Supplemental Table S10). We also noted a positive association between BDE-28 and total lipids (Supplemental Table S11). Sensitivity analyses regarding antihypertensive medication resulted in additional positive associations between BDE-99, PFOS, and PFHxS with diastolic blood pressure (Supplemental Table S12). Results from the BKMR model were consistent with our previous findings (Supplemental Table S13), indicating that the results between EDCs during pregnancy and blood pressure were not consistent between the single- and multi-pollutant models.

4. Discussion

Using data from the HOME Study, we investigated whether EDC biomarkers, including BPA, PBDEs, PFAS, and phthalate metabolites, are associated with cardiometabolic indices during pregnancy using single- and multi-pollutant statistical models. We observed significant positive associations for MEP with systolic and diastolic blood pressure in the single-pollutant anlayses. Multi-pollutant analyses, however, did not identify any EDC as an important contributor to blood pressure. We found that higher concentrations of BDE-28 were associated with higher glucose during pregnancy. This finding was also observed in the BKMR analysis. Significant positive associations were noted between PBDE congeners and cholesterol in both single- and multi-pollutant models. In contrast, MBP and MBzP were associated with significant decreases in cholesterol. However, only MBzP was identified as an important contributor with BKMR in the association with triglycerides, with a U-shaped association. No associations were noted between BPA or PFAS with any cardiometabolic indices during pregnancy across both single- and multi-pollutant models.

While our study reported overall null associations between EDCs and blood pressure during pregnancy based on inconsistent findings between

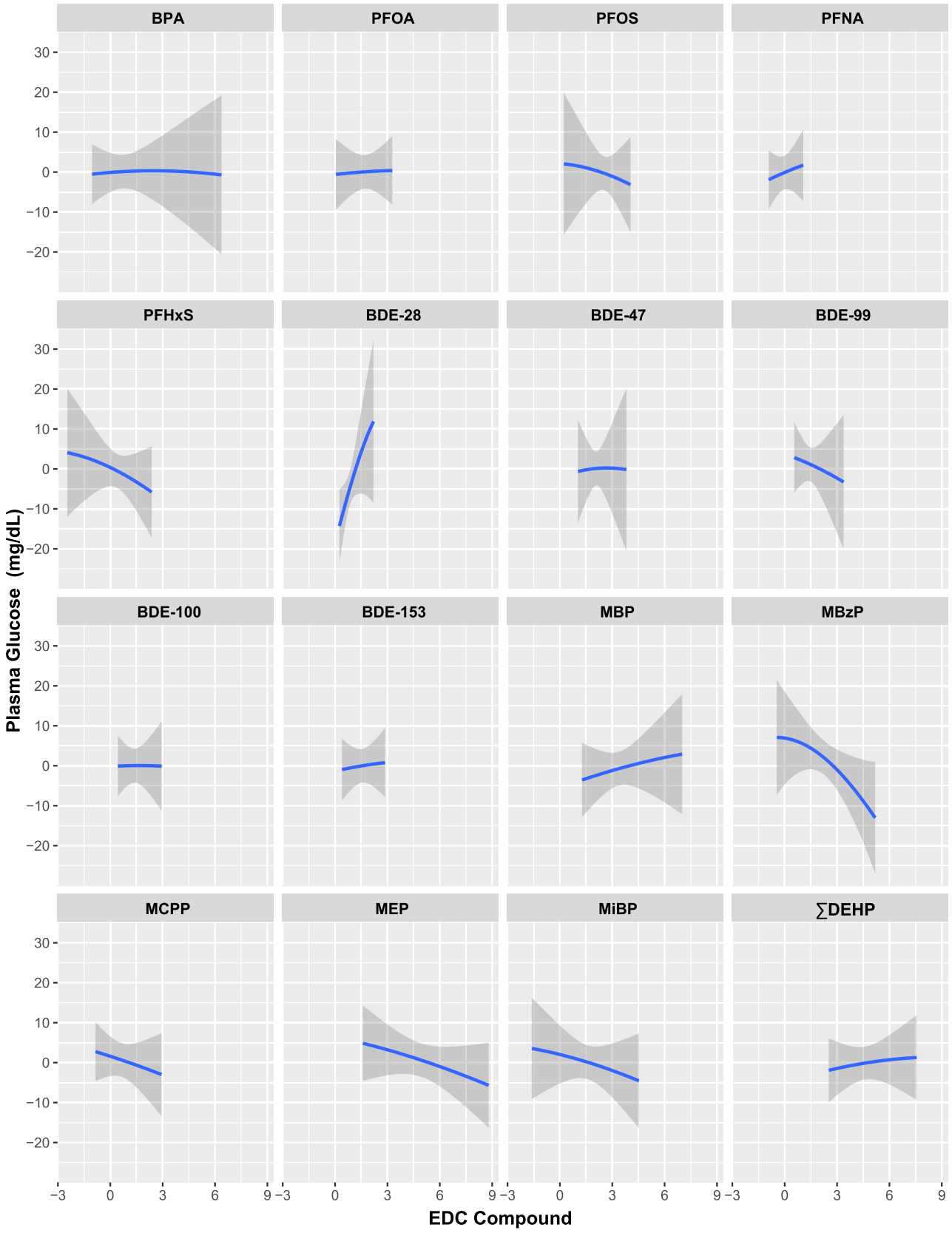

Fig. 1. Exposure response pattern between each EDC (BPA and phthalates at 26 weeks gestation) and glucose levels during pregnancy.

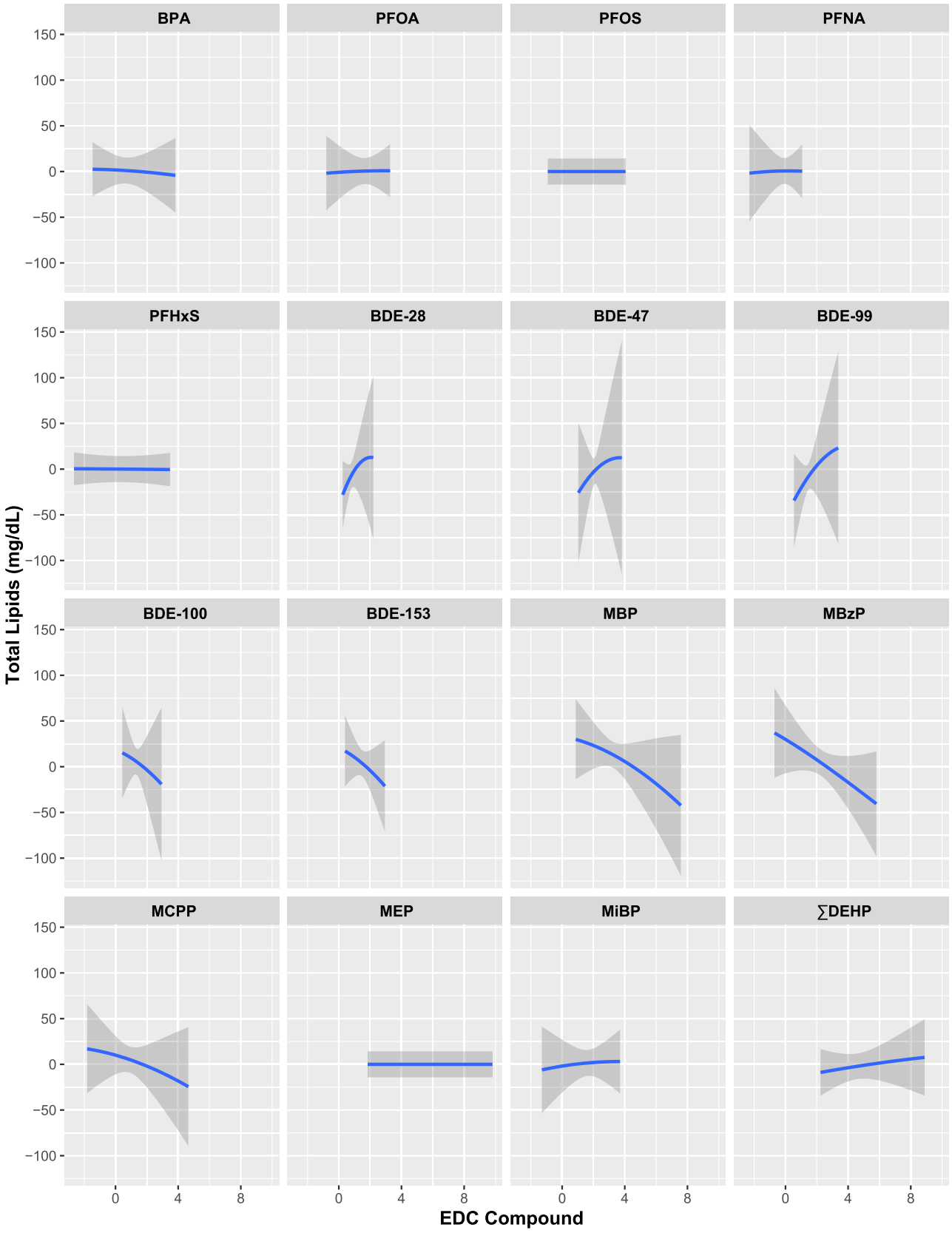

Fig. 2. Exposure response pattern between each EDC at 16 weeks gestation and total lipids during pregnancy.

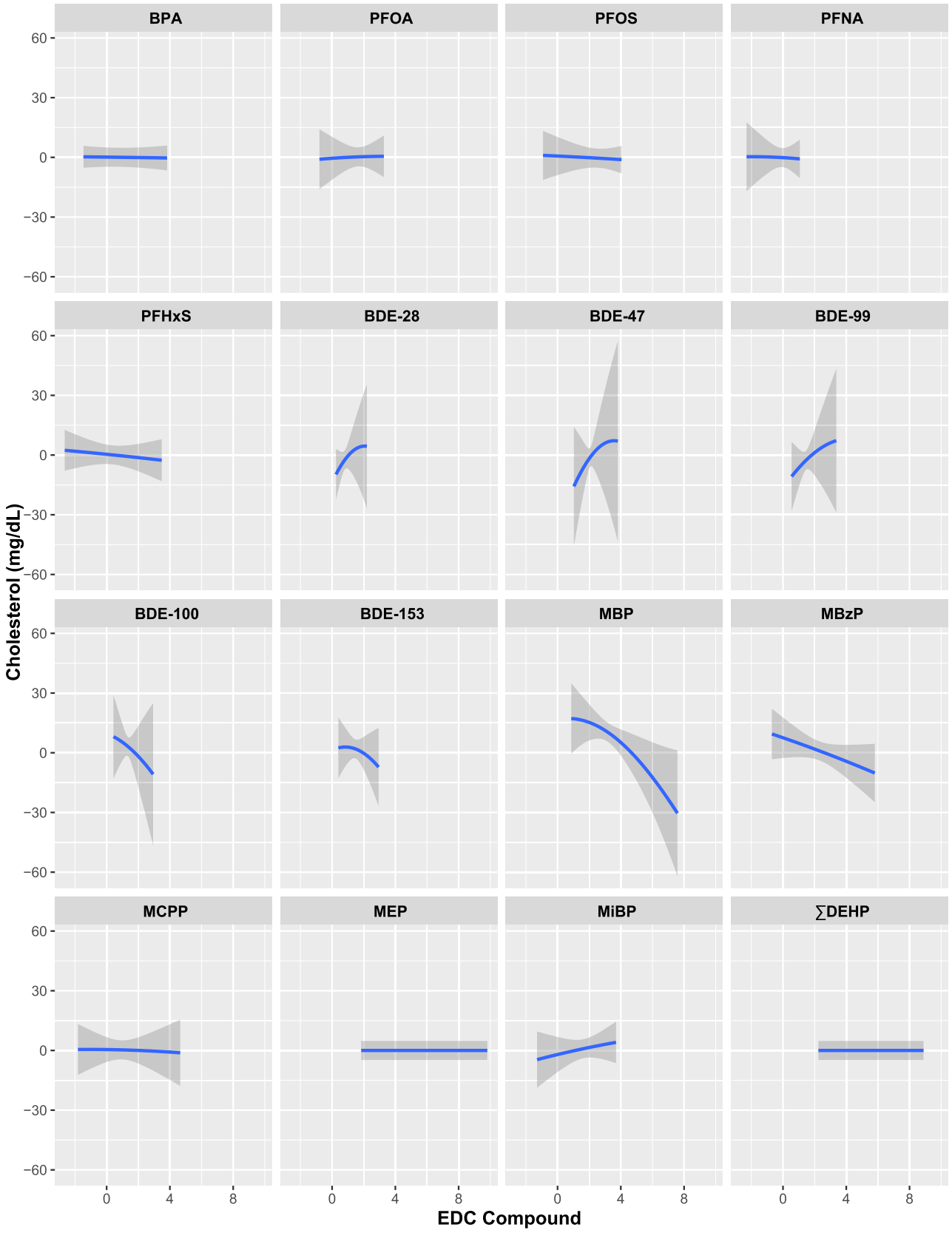

Fig. 3. Exposure response pattern between each EDC at 16 weeks gestation and cholesterol during pregnancy.

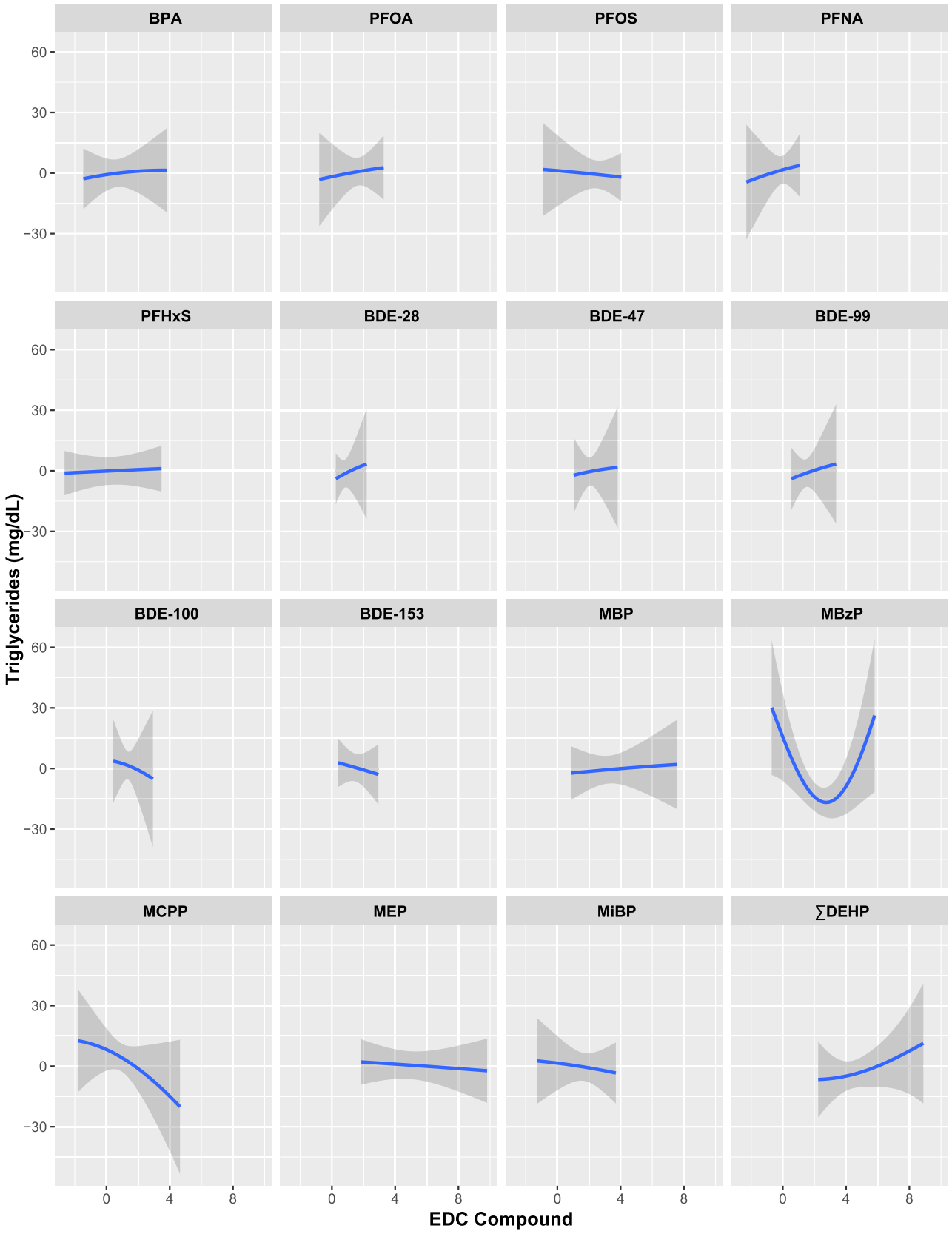

Fig. 4. Exposure response pattern between each EDC at 16 weeks gestation and triglyceride levels during pregnancy.

single- and multi-pollutant models, previous studies found both positive (MBzP, MiBP, PFAS) and negative (BPA, MiBP) associations (Borghese et al., 2020; Han et al., 2020; Warembourg et al., 2019; Werner et al., 2015). Most of the epidemiological studies that investigated EDCs and hypertensive disorders during pregnancy reported discordant conclusions (Camara et al., 2019; Cantonwine et al., 2016; Huang et al., 2019; Rylander et al., 2020; Smarr et al., 2016; Starling et al., 2014; Ye et al., 2017; Wikstrom et al., 2019). Our null finding between BPA and blood pressure may be due to a number of factors, including our modest sample size, the lack of information on prepregnancy hypertension diagnoses, the statistical approaches, and the selection of covariates used in the estimation of associations. Blood pressure measurements also differed between studies. In the present study, we selected to analyze the highest systolic and diastolic blood pressure measurement after 20 weeks gestation since using the highest blood pressure reading may improve the detection of high blood pressure during pregnancy (Whelton et al., 2018). Further, BPA may play a role in hemodynamic changes in pregnancy, but its role may differ between pregnancy-related hypertensive disorders since gestational hypertension and preeclampsia are not conclusively viewed as stemming from the same spectrum (Melamed et al., 2014). Therefore, our examination of blood pressure, rather than a specific pregnancy-related hypertensive disorder, may have contributed to the null associations since blood pressure measures are reflective of more subtle, subclinical changes in vascular function. We were unable to examine gestational hypertension (5.2%), preeclampsia (5.9%), and eclampsia (0%) given the low percentages of HOME Study women with confirmed diagnoses. However, when we examined a composite measure of pregnancy-induced hypertensive disorders we did not observe an association with any EDC compounds.

Previously, the HOME Study reported a significant positive association between urinary MBzP concentrations with diastolic blood pressure and increased risk of pregnancy-induced hypertensive disorders (Werner et al., 2015). Discordant findings may be due to a number of factors, including differences in the timing of phthalates (16 weeks in the present study versus both 16 and 26 weeks in Werner et al.) and blood pressure measurements (the highest blood pressure measurement after 20 weeks gestation in the present study versus blood pressure measurements $<$ 20 weeks and after 20 weeks in Werner et al.), methodology used to examine phthalates (continuous in the present study versus Werner et al.'s analysis of phthalates as continuous and terciles), adjustment of confounders, and statistical methods (single- and multi-pollutant analyses in the present study versus single-pollutant analyses (Werner et al., 2015).

One of our most consistent findings was the positive association between PBDEs and glucose. This conclusion aligns with those reported in the NICHD Fetal Growth Study, the Longitudinal Investigation of Fertility and the Environment (LIFE) Study, and two case control studies - the only four studies to examine this relationship (Eslami et al., 2016; Liu et al., 2018; Rahman et al., 2019; Smarr et al., 2016). A nested case control study in Beijing, China found serum PBDEs during the first trimester of pregnancy were associated with increased fasting blood glucose, 1-hour plasma blood glucose, and 2-hour plasma blood glucose (Liu et al., 2018). Liu et al. additionally reported increased odds of GDM with higher concentrations of BDE-153, BDE-154, and BDE-183 (2018). These conclusions are consistent with the case control study analysis of third trimester total serum PBDEs with GDM risk and the prospective analyses of US women that concluded an increase in the odds of GDM with BDE-47 and BDE-153 (Eslami et al., 2016; Rahman et al., 2019; Smarr et al., 2016).

Toxicological studies provide evidence of PBDEs' potential diabetogenic action. *In vivo* studies observed increased glucose levels following PBDE exposure, with interference of metabolism through oxidative stress and inflammation (Sun et al., 2020; Suvorov et al., 2009). PBDEs have been documented to cause inflammatory reactions, with increases in proinflammatory cytokines interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), and tumor necrosis factor alpha (TNF-α) (Chen et al., 2019; Sun et al., 2020; Rajput et al., 2018; Zhang et al., 2018). Liver damage induced by oxidative stress and inflammation may impair hepatic metabolic capacity. Second, PBDEs may disrupt glucose homeostasis by interfering with the function of pancreatic insulin-producing β cells, which play a role in the establishment of normoglycemia. An *in vitro* study found BDE-47 and BDE-85 directly acts on β cells via the thyroid receptor and Akt activation to stimulate acute insulin secretion (Karandrea et al., 2017). Disturbances in β cell function can result in inadequate insulin secretion and subsequent hyperglycemia, with potential development of hyperinsulinemia (Karandrea et al., 2017). In addition, PBDEs affect several metabolic pathways related to glucose homeostasis, including glycolysis and glucose catabolic processes (Softeland et al., 2011). Rats treated with penta-BDE for 4 weeks had a significant decrease of 59% in insulin-stimulated glucose oxidation compared to controls, demonstrating a metabolic shift through disturbances in insulin signaling (Hoppe and Carey, 2007). Lastly, PBDEs alter thyroid hormones, which are important in metabolic rate (Czerska et al., 2013). Thyroid signaling may play a role in glucose-stimulated insulin secretion (Lenzen et al., 1975; Verga Falzacappa et al., 2007; Verga Falzacappa et al., 2010; Ximenes et al., 2007), and disruptions in thyroid hormones could contribute to hyperglycemia.

Our study found consistent evidence of positive associations between BDE-28, BDE-47, and BDE-99 with total cholesterol in pregnancy across statistical models. A positive association was also found between BDE-28 and total lipids in the BKMR model. However, BDE-153 was identified as having an inverse association with cholesterol in the BKMR model despite null findings in the linear regression model. While no epidemiological study has investigated PBDEs and lipids during pregnancy, a cross-sectional analysis of US adults reported an inverted U-shaped association between BDE-153 and high triglycerides (Lim et al., 2008). BDE-153 was also identified as having a negative association with measures of adiposity in school-aged children with gestational and childhood exposures in the HOME Study (Vuong et al., 2019; Vuong et al., 2016). Findings from the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) Study also concluded BDE-153 reduced BMI and waist *z*-scores in children at 7 years, though these results were only noted with childhood concentrations (Erkin-Cakmak et al., 2015). It is unclear why we observed the discordant directionality of associations in the present study between PBDE congeners and total cholesterol in pregnancy, but our results may be partially due to differences in the toxicokinetics of these congeners. Compared to BDE-47, BDE-99, and BDE-100, congener BDE-153 had the highest distribution in lipophilic tissues five days after intravenous exposure in mice, likely due to BDE-153 having the lowest metabolism and excretion rate (Staskal et al., 2006). BDE-153′s pharmacokinetic properties coupled with its overall lipophilic nature may have contributed to the observed results through reverse causation; BDE-153 may have lower concentrations among individuals with more adipose tissue via "dilution" of concentrations, more so than the other congeners (Chevrier, 2013; Glynn et al., 2003). The positive associations observed between BDE-28, BDE-47, and BDE-99 with cholesterol in the present analyses are supported by evidence from *in vitro* studies suggesting that PBDEs may be potential obesogens. PBDEs have been found to interfere with adipogenic pathways and increase adipocyte differentiation in addition to indirectly affecting weight gain by disrupting thyroid hormones (Bastos Sales et al., 2013; Hoppe and Carey, 2007; Kamstra et al., 2014). However, epidemiological evidence of PBDEs' role as potential obesogens should rely more heavily on studies examining adiposity storage rather than lipids since increases in adipose tissue would be more relevant to the potential obesogenic mechanisms and pathways of PBDEs.

Of the PBDEs examined, we observed consistent positive associations between BDE-28 and a number of cardiometabolic indices, including glucose, cholesterol, and total lipids. While studies investigating the differences in toxicokinetic properties between PBDE congeners are limited, there is some evidence that supports our findings that BDE-28

may play a bigger role in cardiometabolic health. In an *in vivo* study examining PBDEs and oxidative stress in zebrafish, BDE-28 was the only congener found to significantly increase glutathione-*S*-transferase expression and enzymatic activity when compared to BDE-47, BDE-99, and BDE-100 (Usenko et al., 2015). Second, in the HOME Study we previously reported increased concentrations of free and total triiodothyronine (T_3) and thyroxine (T_4) during pregnancy with higher concentrations of BDE-28 and BDE-47 (Vuong et al., 2015). These congeners are more structurally similar to T3 and T4 than BDE-99, BDE-100, and BDE-153. In addition, Tait et al. estimated the relative toxicity of eight PBDEs (BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183, and BDE-209) using human liver and colon cell lines and reported the highest Toxicological Prioritization Index (ToxPi) score for BDE-153 and BDE-28 (2017). Further, BDE-28 had the highest permeability coefficient of all the PBDE congeners, indicating rapid absorption (Tait et al., 2017).

We found that MBzP had a negative association with cholesterol in the single-pollutant model and was an important contributor in the BKMR model examining triglycerides, displaying a U-shaped distribution. Our findings align with the only other epidemiological study to examine phthalates and lipids, specifically triglycerides and fatty acid levels in pregnancy using the Hokkaido Study on Environment and Children's Health (Jia et al., 2015). Jia et al. reported lower triglycerides and four fatty acids (palmitic, oleic, linoleic, and α-linolenic acids) with higher MEHP concentrations measured at 32–34 weeks gestation in maternal blood (2015). The inverse associations noted in both studies are concordant with those reported in rats and pregnant mice describing hypotriglyceridemic effects following DEHP exposure (Dirven et al., 1990; Hayashi et al., 2011; Oishi, 1984; Reddy et al., 1976; Sakurai et al., 1978). Phthalates may produce hypolipidemic effects through signaling of peroxisome proliferation-activated receptor α (PPAR-α)-dependent fatty acid catabolism via hepatic oxidative metabolism and microsomal triglyceride transport (Feige et al., 2010; Hayashi et al., 2011). Alternatively, these inverse associations may also be influenced by unmeasured confounders that may play a role in the relationship between phthalates and lipids.

Our study had several strengths, foremost of which is the availability of both EDCs and cardiometabolic measurements in a well-established pregnancy and birth cohort. We were able to assess ubiquitous EDCs of potential obesogenic and diabetogenic concern quantified during pregnancy, including BPA, PBDEs, PFAS, and phthalates. Further, we included several cardiometabolic indices, such as blood pressure, glucose, and lipids during pregnancy. Second, we adjusted for an extensive array of potential confounders, including sociodemographics, behavioral factors, serum ∑PCBs, prepregnancy BMI, and parity. We additionally performed sensitivity analyses taking into account intake of fruits and vegetables and removing prepregnancy BMI from models to ensure conclusions did not differ. Lastly, we modeled EDCs using both single- and multi-pollutant models to reach balanced conclusions while taking into account potential interactive effects between EDCs in each of the potential associations with cardiometabolic indices.

Our findings are subject to a number of limitations. We do not have information regarding a diagnosis of chronic hypertension within the HOME Study. As such, we relied on self-reported use of antihypertensive medications as a proxy measure of prepregnancy hypertension. This information was used to perform three separate sensitivity analyses, including adjusting for hypertensive medication usage, taking into account treatment effects of antihypertensive medications on blood pressure measures, and removing women who reported antihypertensive medications from the analyses, all of which confirmed our primary conclusions that the associations were not consistent between the single- and multipollutant models for EDCs and blood pressure during pregnancy. We had information on fruit and vegetable intake during pregnancy, but we lacked information on full dietary intake. In addition, residual confounding from other unmeasured risk factors is possible. Fourth, BPA and phthalates are non-persistent EDCs whose urinary biomarkers have moderate to high within-person variability, which may lead to non-differential exposure misclassification. However, we measured these biomarkers at two time points during pregnancy and any non-differential exposure misclassification is expected to bias our results toward the null. Further, PFAS were analyzed as an average during pregnancy in the primary analyses. To ensure there were no differences in our study's final conclusions, we additionally analyzed PFAS concentrations measured only at 16 weeks gestation and observed similar results, alleviating concerns of potential exposure misclassification of PFAS. Fifth, we were unable to evaluate the associations between EDCs and several well-recognized predictors of future cardiometabolic health, such as preeclampsia (5.9%), gestational hypertension (5.2%), and GDM (3.6%), due to low numbers in the HOME Study. Lastly, we relied on chart-derived measures, which may be subject to misclassification bias.

5. Conclusion

In conclusion, our findings provide further evidence to support that PBDEs and phthalates may be associated with cardiometabolic indices in pregnant women. We observed positive associations between BDE-28 with glucose during pregnancy, suggesting PBDEs may play a role in disrupting normoglycemia. We also found that several PBDE congeners were associated with higher total cholesterol, though BDE-153 displayed a significant inverse association. Disparate associations between PBDE congeners with total cholesterol may be due to differences in physiochemical and toxicokinetic properties. Lower cholesterol levels were further observed with increased concentrations of MBP and MBzP. In addition, MBzP had a U-shaped relationship with triglycerides in the BKMR model. No consistent associations were noted between any EDC biomarker and blood pressure during pregnancy, nor was there sufficient evidence to suggest BPA or PFAS are associated with any of the analyzed cardiometabolic indices during pregnancy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106747.

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