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Association between persistent endocrine-disrupting chemicals (PBDEs, OH-PBDEs, PCBs, and PFASs) and biomarkers of inflammation and cellular aging during pregnancy and postpartum

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Abstract

Background—Endocrine-disrupting chemicals (EDCs) can target immune and metabolic pathways. However, few epidemiologic studies have examined the influence of EDCs on measures of inflammation and cellular aging during pregnancy and postpartum.

Objective—We investigated associations between prenatal exposures to polybrominated diphenyl ethers (PBDEs), hydroxylated PBDE metabolites (OH-PBDEs), polychlorinated biphenyls (PCBs), and per- and polyfluorochemicals (PFASs) with repeated biomarker measurements of inflammation and cellular aging in women during pregnancy and the postpartum period.

Methodology—Overweight or obese pregnant women were recruited from the San Francisco Bay area (n=103) during their first or second trimester of pregnancy. Blood samples were collected from participants at baseline (median 16 weeks gestation) and at three and nine months postpartum. Serum concentrations of PBDEs, OH-PBDEs, PCBs, and PFASs were measured at baseline. Inflammation biomarkers (interleukin 6 [IL-6], interleukin 10 [IL-10], and tumor

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necrosis factor [TNF-α]) and leukocyte telomere length (LTL), a biomarker of cellular aging, were measured at all three time points. Associations between serum chemical concentrations and repeated measures of IL-6, IL-10, TNF-α, and LTL were examined using linear mixed models. We also examined the potential for effect modification by time (visit) and obesity.

Results—In adjusted models, we observed positive relationships between PBDEs and proinflammatory cytokines (IL-6 and TNF-α). A doubling in ΣPBDEs was associated with a 15.26% (95% CI 1.24, 31.22) and 3.74% (95% CI −0.19, 7.82) increase in IL-6 and TNF-α, respectively. Positive associations were also observed for PFASs and IL-6. A two-fold increase in ΣPFASs was associated with a 20.87% (95% CI 3.46, 41.22) increase in IL-6. 5-OHBDE-47 was inversely associated with anti-inflammatory cytokine IL-10. Some EDC-outcome associations, including those of PBDEs with TNF-α, were stronger during pregnancy (compared three or nine months postpartum) and among obese (compared to overweight) women (p-interaction < 0.05).

Conclusions—These findings suggest that exposure to specific EDCs is associated with increased inflammation among women during pregnancy and the postpartum period. Future studies should replicate these findings in additional study populations and examine the implications of these associations for maternal and child health.

Keywords

Polybrominated diphenyl ethers; per- and polyfluorochemicals; leukocyte telomere length; pregnancy; environmental chemicals; prenatal exposures

1. Introduction

Over the past several decades, halogenated chemicals, such as polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyl ethers (PCBs), and per- and polyfluorochemicals (PFASs), have been widely used in consumer products, leading to ubiquitous human exposure.[1, 2] PBDEs were used as flame retardants in upholstered furniture, electronics, and textiles until they were phased out of use in the US around 2004.[3] PCBs were once widely used as lubricants and coolants, and now persist in the environment despite being banned in 1979.[4] PFASs are used to impart water and stain resistance to products such as upholstery, non-stick cookware, and food packaging.[5] While two specific PFAS chemicals, PFOA and PFOS, have been subject to several manufacturing and use restrictions, other PFASs are still commonly used in the US.[6] All three chemical classes have long elimination half-lives in the body;[7–9] may persist in the indoor environment;[10, 11] and can biomagnify in the food web.[12] PBDEs and PCBs are lipophilic while PFASs preferentially bind to proteins such as albumin.[13] Among US populations, serum concentrations of PCBs declined after their phase-out but have plateaued in recent years.[14, 15] Exposures to PBDEs and PFASs have also declined after their market phase-out.[14, 16] Nevertheless, these chemicals are routinely detected in pregnant and lactating women.[1, 17, 18]

Regulatory and scientific communities are concerned about the public health consequences of PBDEs, their hydroxylated metabolites (OH-PBDEs), PCBs, and PFASs in part because they are endocrine disrupting chemicals (EDCs) that can interfere with the action of multiple hormones including estrogen, androgen, and thyroid hormones.[19, 20] For both women and

their offspring, pregnancy and early postnatal life represent vulnerable periods for high sensitivity to EDC exposures.[20–23] Indeed, higher levels of EDCs during pregnancy have been associated with changes in thyroid hormone levels in pregnant women,[24–27] as well as adverse birth outcomes, and neurodevelopmental harm in their offspring.[28, 29]

EDCs may also increase disease risks through induction of oxidative stress and inflammation.[30, 31] PBDEs and OH-PBDEs show antagonistic activity towards the glucocorticoid receptor,[32, 33] which can promote chronic inflammation.[34, 35] *In vitro* studies of human placental cells demonstrate increased secretion of pro-inflammatory cytokine IL-6 and decreased secretion of anti-inflammatory cytokine IL-10 when treated with BDE-47, the most biologically ubiquitous PBDE congener.[36, 37] *In vitro* and *in vivo* studies suggest that PFOA and PFOS can alter the inflammatory response, although the specific effects vary by exposure route and dose.[38] In a cross-sectional study of the US general population, exposures to certain PBDE congeners were positively associated with some inflammation biomarkers.[39]

Oxidative stress and inflammation can also influence regulation of telomeres,[40, 41] non-coding segments of DNA found at the ends of chromosomes that may be a novel biomarker of EDC toxicity.[42] Because telomeres are shortened with every cell division, eventually reaching a critical length that triggers cell senescence, they are considered a measure of cellular aging.[42, 43] Although telomeres typically shorten over the life of a cell, under certain circumstances telomeres can elongate.[43] Leukocyte telomere length (LTL) in blood is commonly measured in epidemiological studies.[44–46] Exposure to some environmental chemicals may influence LTL, with both positive and inverse associations reported in the literature.[47–50] For example, several cross-sectional studies have found an association between serum concentrations of PCBs and longer LTL in adults.[46, 51, 52]

Despite this evidence, no prior epidemiologic study, to our knowledge, has investigated associations between persistent, halogenated EDCs and measures of inflammation and cellular aging in pregnant women. Accordingly, our study objective is to examine the association between prenatal serum concentrations of PBDEs, OH-PBDEs, PCBs, and PFASs and repeated measures of inflammation and LTL during pregnancy and postpartum among a cohort of ethnically diverse, lower-income, overweight or obese women.

2. Methods

2. 1 Study Population

Between 2011 and 2013, overweight and obese pregnant women were recruited in the first or second trimester of pregnancy from prenatal clinics and community centers in the San Francisco Bay area for participation in the Maternal Adiposity, Metabolism, and Stress Study (MAMAS). The MAMAS study was an 8-week mindful eating intervention aimed at reducing stress and preventing weight gain during pregnancy. The intervention was registered at clinicaltrials.gov as NCT01307683. Recruitment and retention methods have been previously described.[53] Subjects were eligible for inclusion in the MAMAS study if the following criteria were met: 18–45 years old, 8–23 weeks pregnant, singleton pregnancy, a household income <500% of the federal poverty level, English-speaking, and a self-reported,

pre-pregnancy body mass index (BMI) between 25.0–40.0 kg/m^2. Pre-pregnancy BMI was later confirmed with medical records; there were seven participants with a pre-pregnancy BMI <25 (BMI between 23.0 and 25.0) and three participants with a BMI>40 (BMI between 40.0 and 42.1). These women were retained in the intervention study. Estimated delivery date and gestational age were self-reported at screening and later confirmed with medical records. In most cases, the estimated delivery date was based on last menstrual period and early ultrasound measurements. Subjects were excluded if they had preexisting conditions that interfered with baseline body composition such as polycystic ovarian syndrome, eating disorder, or diabetes. Participants were followed from enrollment through nine months postpartum. The analytic sample for this study is comprised of 103 women in the intervention group with complete data on EDC concentrations and lipid content measured at baseline. Availability of data differed by outcome biomarker and by visit. A summary of participant eligibility and data completeness is provided in Supplemental Materials (Figure S1). Informed consent was obtained from all study participants. The University of California, San Francisco (UCSF) Committee on Human Research and the California Pacific Medical Center Institutional Review Board approved the study protocols.

2.2 Sample Collection and Preparation

Fasting blood draw samples were collected from participants at baseline, three months postpartum, and nine months postpartum by UCSF Clinical Research Center staff who were certified in phlebotomy. The median and range of gestational/postpartum weeks of women at the time of each blood draw were as follows: baseline (16 weeks gestation [10 – 24]; 3 months postpartum (14 weeks postpartum [11 – 22]; and 9 months postpartum (39 weeks postpartum [37 – 46]. For measurement of EDCs, maternal blood was collected in red vacutainer tubes. Blood was allowed to clot for 60 minutes, and then placed on ice. Samples were centrifuged at 1300g for 10 minutes at 4°C, and then the sera were aliquoted into vials. For measurement of inflammation biomarkers, maternal blood was collected in purple EDTA tubes. Samples were centrifuged at 1300g for 10 minutes at 4°C, and then the plasma were aliquoted into vials. For measurement of telomere length, whole blood was collected in a glass blood collection tube with acid citrate dextrose. All samples were stored at −80°C until further analysis.

2.3.1 Environmental Chemical Analysis and Lipid Determination

Environmental chemical concentrations in serum were measured in participants at baseline. All chemical analyses were conducted at the Department of Toxic Substances Control (Berkeley, CA, USA) within its laboratory facility, where human specimens are exclusively processed. This study focuses on individual chemicals (four PBDEs, three PCBs, five PFASs, and two OH-PBDEs) that were detected in at least 50% of the study population.

The PFAS analysis method has been previously described.[54] In summary, 100 μL of human serum were spiked with 10 isotope-labeled (^{18}O or^{13}C) internal standards and denatured with formic acid. Then the samples were directly injected into an online SPE-LC/MS system; first extracted using SPE C18 cartridges, then after washing, the analytes were eluted to the LC/MS for further analysis. LC/MS analysis was performed on an ABSciex

4000 qtrap system with a BETASIL 50 mm C8 HPLC column. The data are reported as ng/mL in serum. Eleven PFASs were successfully quantified in these samples.

For PBDEs, OH-PBDEs, and PCBs, the liquid-liquid extraction and the method used to separate the phenolic compounds from neutral compounds is described in detail elsewhere. Once separated, OH-PBDEs were methylated with diazomethane and transformation yield was evaluated with $^{13}C_{12}$ 6-OH-BDE47 (Wellington Labs, Guelph Ontario, Canada). In separate analytical runs, nineteen PBDEs and eight OH-PBDEs were separated with a DB-5MS column (15 m × 0.25 mm I.D. × 0.25 μm film thickness, J & W Scientific, Folsom, CA). Compounds were quantified using gas chromatography/high resolution double-focusing sector mass spectrometry (GC-HRMS, DFS, ThermoFisher, Bremen, Germany) with isotope dilution.

Fifteen PCBs were quantified using gas chromatography/triple-quadrupole tandem mass spectrometry (GC-MS/MS, Agilent, Santa Clara, CA) equipped with a 30m DB-5ms column (Agilent) and a 24-minute run time. Concentrations were recovery corrected with sixteen isotopically-labeled surrogate standards (listed in Supplemental Materials, Table S1). Lipid analysis for serum was completed at Boston Children's Hospital. Total lipid content was calculated from measurements of total cholesterol and triglycerides using Phillips' formula.[55]

The instrument detection threshold (IDT) was defined according to the peak height/area. The method detection limit (MDL) was calculated as three times the standard deviation (SD) of the blank concentrations. Standard reference material (SRM 1958, National Institute of Standards and Technology, Gaithersburg, MD) and pre-spiked bovine serum with known amounts of target analytes were used to calculate precision and accuracy. All were within reasonable analytical error ranges (Supplemental Materials, Table S1).

We imputed values below the MDL using a log-normal probability distribution whose parameters were calculated using maximum likelihood estimation.[27, 56, 57] Concentrations for PBDE and PCB concentrations were normalized for lipid content (ng/g lipid), and OH-PBDEs and PFASs were expressed as wet weights (ng/mL). In addition to examining chemical analytes individually, we also constructed the following four summary measures: the sum of BDE-47, BDE-99, BDE-100, and BDE-153 (ΣPBDEs), the sum of PCB-138, PCB-153, and PCB-180 (ΣPCBs), the sum of PFOS, PFOA, PFHxS, PFNA, and PFDeA (ΣPFASs), and the sum of 5-OHBDE-47 and 6-OHBDE-47 (ΣOH-PBDEs).

2.4 Inflammation and Cellular Aging Biomarkers

Plasma concentrations of IL-6, IL-10, and TNF-α were measured using the Meso Scale Discovery Multi-Spot human cytokine assay system (Rockville, MD) according to manufacturer's directions at University of California, Davis. The lower limit of detection (LLOD), defined as the calculated concentration corresponding to the signal 2.5 standard deviations above the background, was: IL-6 (0.06 pg/ml), IL-10 (0.03 pg/ml), TNF-α (0.04 pg/ml). LTL was measured using the quantitative polymerase chain reaction method to measure telomere length relative to standard reference DNA (T/S ratio).[58] Methods for the analysis of LTL in the MAMAS cohort has been described in detail elsewhere.[59]

2.5 Measurement of Covariates

Information on maternal age at enrollment, race/ethnicity, educational attainment, marital status, income, parity, and smoking history were obtained by questionnaire at the baseline visit. To calculate BMI (kg/m^2), research staff measured weight and height at baseline and at the three months postpartum and nine months postpartum visits. Gestational age at enrollment and time from delivery were calculated based on expected delivery date and infant date of birth, respectively, obtained from medical records.

2.6 Statistical Analysis

Descriptive statistics (geometric mean [GM], geometric standard deviation [GSD], median, and 95th percentile estimates) were calculated for all PBDEs, OH-PBDEs, PCBs, and PFASs with ≥50% detection frequency. We assessed the correlations between chemical class sums using Spearman correlations.

The distribution of outcome biomarker measurements at each time point was assessed using boxplots.[60] GM (GSD) were calculated for each outcome biomarker within strata of the demographic variables at baseline and differences between groups were tested using analysis of variance (ANOVA). Spearman correlation was used to analyze correlations within the individual outcome biomarkers over time, and between the different outcome biomarkers. Additionally, temporal variability in outcome biomarker measurements was examined using intraclass correlation coefficients (ICCs).

All chemical and biomarker measurements were natural log-transformed prior to regression analyses to account for non-normal distributions. Unadjusted scatterplots of EDC concentrations and outcome biomarker measurements at each visit were superimposed with a lowess curve to assess the shape of the exposure-response relationships. These plots generally suggested linear associations. Accordingly, most chemicals were modeled as continuous variables. However, based on observed associations and the lower detection frequencies, 5-OHBDE-47, 6-OHBDE-47, ΣOH-PBDEs, PCB-138, and PCB-180 were modeled as categorical variables (< MDL; > MDL and ≤ median of detected values; and > median of detected values).

Multivariable mixed-effect generalized linear models were fitted to assess the longitudinal associations between individual and summary measures of EDCs and outcome biomarker measurements. Random intercepts were used to account for within-subject correlation. An exchangeable correlation matrix and robust standard error estimation were used. Visit number was included as a nominal categorical variable in mixed models to account for time. We examined model fit through examination of residual plots and residual diagnostics. For EDCs modeled as continuous variables, percent difference in IL-6, IL-10, TNF-α, and LTL for a doubling of EDC concentration was calculated as $(\exp(\ln 2 \times \beta) - 1) \times 100\%$, with the 95% confidence intervals (CIs) estimated as $(\exp[\ln 2 \times (\beta \pm 1.96 \times SE)] - 1) \times 100\%$.[61] For EDCs modeled as categorical variables, percent difference in IL-6, IL-10, TNF-α, and LTL comparing an EDC concentration to the referent category (below MDL) was calculated as $(\exp(\beta) - 1) \times 100\%$, with the 95% confidence intervals (CIs) estimated as $(\exp(\beta \pm 1.96 \times SE) - 1) \times 100\%$.[61] In cross-sectional models, the percent difference 95% CIs were

calculated using the exact critical value (based on a t distribution with N-2 degrees of freedom and an upper tail area of 0.025) in place of 1.96 due to smaller sample size.

Covariates examined included age at enrollment (continuous), time-varying BMI (continuous), race/ethnicity (White, Other, or Multiracial; African American; or Latina), educational attainment (≤ high school or > high school), marital status (married/long-term relationship or other), gestational age at baseline (weeks; continuous), parity (0 or >1), and smoking status (current/former or never). Age, race/ethnicity, and BMI were included in the models *a priori*, while additional covariates were incorporated using a 10% change-in-estimate approach. Statistical analyses were conducted using Stata software 13.0 (StataCorp, College Station, TX). A p-value <0.05 was used to designate statistical significance using two-sided tests.

We assessed the potential for effect modification by obesity by including an interaction term for EDC and obesity (BMI <30 vs. BMI ≥30) in adjusted mixed models. To assess whether associations between EDC concentrations and biomarker outcome measurements varied over time, we qualitatively examined cross-sectional associations between the EDC concentrations and outcome biomarker measurements at each time point. Model fit was assessed by examining studentized residuals from the adjusted cross-sectional models. We then included an interaction term for EDC and visit number in our adjusted mixed models. In both interaction analyses, we examined the statistical significance of the main effect for chemical and the global significance of the interaction terms using a significance level of 0.05.

We used two approaches to account for potential correlation between categories of EDCs. (1) The sums of other EDC classes were added as covariates to each multivariable mixed model. For example, models using individual PBDE congeners or ΣPBDEs as the exposure measure were mutually adjusted for ΣOH-PBDEs, ΣPCBs, and ΣPFASs. The percent difference estimates for each category sum were obtained from a single multivariable mixed model in which all category sums (ΣPBDEs, ΣPCBs, ΣPFASs, and ΣOH-PBDEs) were entered. (2) We conducted weighted quantile sum (WQS) regression[62] using data from baseline visit only to estimate the association of cumulative chemical exposure with the outcome biomarkers, using the R package gWQS. The WQS models were adjusted for all variables in the main models (except for visit); four chemical quantiles and a 40/60 split for training/validation were used. We performed 100 bootstrapping steps and focused on the direction of increased risk (positive betas).

2.7 Sensitivity Analyses

Several sensitivity analyses were implemented to assess the robustness of our main findings. (1) To assess sensitivity to the method of lipid adjustment, we re-fitted the adjusted mixed models using log-transformed PBDEs and PCBs as the exposure with log-transformed lipid measurement as a covariate. (2) To assess sensitivity to the operationalization of race, Other/Multiracial and White were modeled as separate categories. (3) Multiple imputation was used for missing values of smoking to assess whether results were sensitive to these missing data. Logistic regression was used to impute values of smoking (ever or never) modeled as a function of age at enrollment, marital status, BMI at baseline, education, and parity. Five

imputations were carried out, and coefficients and standard errors were adjusted for variability between imputations using Rubin's procedures.[63] (4) To assess sensitivity to extreme biomarker values, three participants with large (absolute value >3) studentized residuals for TNF-α at three months postpartum were excluded from the multivariable mixed-effect models.

3. Results

3.1 Descriptive Statistics for Demographics, Serum EDC Concentrations, and Outcome Biomarker Measurements

Among the four classes of EDCs examined, PBDEs and PFASs were most frequently detected. Three chemicals were detected in 100% of participants (BDE-47, PFOS, and PFNA) and an additional five EDCs were detected in >85% of participants (BDE-99, BDE-153, PCB-153, PFOA, and PFHxS) (Table 1). One hundred percent of IL-10 and TNF-α concentrations were above the LLOD, and 99.3% were above the LLOD for IL-6 (not shown). ΣPBDEs was positively associated with ΣOH-PBDEs (Spearman $r_s = 0.54$, $p < 0.0001$) and negatively associated with ΣPFASs (Spearman $r_s = -0.24$, $p = 0.02$). The remaining associations between chemical class sums were weak and non-significant. Sociodemographic and biological determinants of chemical exposures in this cohort along with correlations between individual chemicals will be further described in a companion manuscript (under preparation).

GM and GSD of IL-6, IL-10, TNF-α, and LTL measured at the baseline visit, and within strata defined by demographic characteristics, are presented in Table 2. The mean (SD) age at enrollment was 27.9 (5.7) years old. The study population was comprised of overweight or obese low-income pregnant women (mean [SD] BMI at second trimester visit: 31.5 [4.3]). The majority of participants were non-white (86%) and were married or in a committed relationship (67%). About half (49%) of the subjects were nulliparous and few (5%) were current cigarette smokers. Serum IL-6 concentrations differed significantly by race/ethnicity, BMI category, marital status, and poverty level. Measurements of IL-10, TNF-α, and LTL were generally similar across levels of covariates, with the exception of age at enrollment, which was inversely associated with IL-10. Biomarker measurements did not significantly differ over time for IL-6, IL-10, or LTL (Figure 1). The median (IQR) concentration of TNF-α was 1.85 (1.59, 2.05) pg/mL at second trimester, 2.01 (1.77, 2.41) pg/mL at three months postpartum, and 1.97 (1.69, 2.34) pg/mL at nine months postpartum (Supplemental Materials, Table S2).

Correlations of the outcome biomarkers across time (Figure 2) revealed that LTL measurements were most strongly correlated across time (Spearman r_s range 0.86 to 0.91, all pairwise $p < 0.0001$), while IL-10 was mostly weakly correlated across time (Spearman r_s range 0.36 to 0.42, all pairwise $p < 0.005$). Similarly, the highest ICC was observed for LTL (ICC = 0.90) and the lowest ICC was observed for IL-10 (ICC = 0.37); the ICCs of IL-6 and TNF-α were 0.71 and 0.63, respectively (Table S2). Correlations between biomarkers were weak to moderate. The strongest positive correlation across biomarkers was between IL-10 and TNF-α (Spearman r_s range 0.30 to 0.48, all pairwise $p < 0.01$), and the strongest

negative correlation was between TNF-α and LTL (Spearman r_s range −0.37 to −0.25, all pairwise $p < 0.05$).

3.2 Associations of Serum EDC Concentrations with Outcome Biomarker Measurements

EDCs from multiple chemical classes were positively associated with IL-6 and TNF-α in the mixed-effect models (Table 3). For example, we observed 15.26% (95% CI 1.24, 31.22) and 3.74% (95% CI −0.19, 7.82) increases in IL-6 and TNF-α, respectively, for a doubling of ΣPBDEs. Compared to 6-OHBDE-47 below MDL, the highest tertile of 6-OHBDE-47 was associated with 51.06% (15.45%, 97.66%) higher concentration of IL-6 (p trend = 0.02). PFOS, PFOA, and ΣPFASs were also positively associated with IL-6. For example, a doubling of ΣPFASs concentrations was associated with a 20.87% (95 CI 3.46, 41.22) increase in IL-6. Few statistically significant associations were found between EDCs and IL-10 or LTL. 5-OHBDE-47 was inversely associated with IL-10 (p trend = 0.02), and the highest tertile of 5-OHBDE-47 exposure was associated with −25.81% (95% CI −38.64, −10.29%) difference in IL-10.

In adjusted mixed models with an interaction term for chemical concentration and obesity (BMI <30 vs. BMI ≥ 30), some EDC-outcome associations were found to differ significantly by obesity (Figure 3, Tables S3–S6). In all cases of significant interaction, the EDC-outcome associations were positive among obese women and null among overweight women. For example, a two-fold increase in PFDeA was associated with a 16.02% (95% CI 3.55, 30.00) increase in IL-6 among obese women and with a −4.11% (95% CI −15.38, 8.66) percent change in IL-6 among overweight women. BDE-47, BDE-100, and ΣPBDEs were significantly associated with increased TNF-α, and BDE-153 was associated with increased LTL, among obese but not among overweight women.

Results from adjusted cross-sectional analyses of associations of serum EDC concentrations with outcome biomarker measurements are presented in Tables S7–S10 (Supplemental Material). Studentized residuals from adjusted cross-sectional models indicated appropriate model fit. In cross-sectional models, associations of PBDEs with IL-6 varied over time and were most pronounced during pregnancy. All four PBDEs were significantly associated with increased IL-6 at second trimester but associations were attenuated at three months postpartum; only BDE-153 was significantly associated with IL-6 at nine months postpartum (Table S7). Similarly, BDE-47, BDE-99, BDE-100, and ΣPBDEs were significantly associated with increased TNF-α at second trimester but not at three months postpartum or nine months postpartum (Table S9). In contrast, the highest tertile of 5-OHBDE-47 was associated with a significant decrease in LTL (−11.06% [95% CI −18.52, −2.90]) at 9 months postpartum (Table S10). In multivariable mixed-effect models with an interaction term for chemical concentration and time, EDC-outcome associations were found to significantly differ by visit only for PBDEs and TNF-α (Figure 4).

Adjustment for the sums of other EDC classes resulted in meaningful differences for multiple chemical-biomarker associations (Figure 5, Table S11). Associations between PBDEs and IL-6 and TNF-α were generally of higher magnitude after adjustment for other chemical classes, and more statistically significant associations were observed. A two-fold increase in ΣPBDEs was associated with 21.70% (95% CI 4.33, 41.97) higher IL-6

concentration after adjustment for other EDC classes, compared to a percent difference of 15.26% (95% CI 1.24, 31.22) estimated in the original analysis. The estimated associations of PFASs with IL-6 also generally increased after adjustment for other chemical classes. A two-fold increase in ΣPFASs was associated with 25.73% (95% CI 7.81, 46.64) higher IL-6 concentration after adjustment for other EDC classes, compared to a percent difference of 20.87% (95% CI 3.46, 41.22) estimated in the original analysis. WQS regression identified PFNA and PFDeA as the most potently associated with IL-6 at baseline; these chemicals contributed 16% and 13% of the WQS index weight, respectively (Figure S2). A two-fold increase in the chemical index was associated with 36.20% increase in IL-6 concentration (95% CI 4.73, 77.12). The WQS index was not significantly associated with IL-10, TNF-α, or LTL at baseline.

3.3 Sensitivity Analyses

Across sensitivity analyses, associations of PBDEs with IL-6 and TNF-α remained stable, but some associations that were non-significant in the main results became significant and vice versa. For example, the association of ΣPBDEs with TNF-α was statistically significant in sensitivity analyses for categorization of race/ethnicity (4.03% [95% CI 0.15, 8.05], Table S13) and multiple imputation for missing values of smoking (3.93% [95% CI 0.05, 7.95], Table S14), although non-significant in the main model (3.74% [95% CI −0.19, 7.82]).

For lipid-adjusted EDCs that were modeled as continuous variables (i.e., PBDEs, PCB-153 and ΣPCBs), results were not sensitive to the method of lipid adjustment (Supplemental Material, Table S12). For lipid-adjusted EDCs that were modeled as categorical variables (i.e., PCB-138 and PCB-180), some results changed when lipid measurements were included as a separate covariate. For example, the highest tertile of PCB-180 exposure was associated with −21.36% (95% CI −46.02, 14.58) change in IL-6 when lipid was included as a covariate, compared to −12.85% (95% CI −38.79, 24.09) in the main model, although neither effect was significant.

Results were not sensitive to the categorization of race/ethnicity (Supplemental Material, Table S13). Multiple imputation for missing values of smoking did not qualitatively change results (Supplemental Material, Table S14). For EDCs modeled as continuous variables (PBDEs, PCB-153, and PFASs), results were generally not sensitive to multiple imputation for missing values of smoking. For EDCs modeled as categorical variables (PCB-138, PCB-180, and OH-PBDEs), some changes in effect estimates were observed among non-significant associations only. Exclusion of three participants with extreme values of TNF-α at three months postpartum did not qualitatively change results (not shown).

4. Discussion

In this longitudinal study of predominantly non-white, low-income, overweight or obese California women, we examined associations between prenatal exposures to several classes of consumer product chemicals and repeated measures of inflammation and cellular aging biomarkers across pregnancy and postpartum. We found significant positive associations between some PBDE and OH-PBDE analytes and levels of pro-inflammatory cytokines (IL-6 and TNF-α), as well as between some PFASs and IL-6. There were few consistent

associations between EDCs and measures of IL-10 or LTL. These findings suggest that exposure to certain EDCs may be associated with inflammation during pregnancy, although additional epidemiological and mechanistic studies are warranted.

Serum concentrations of PBDEs in this population are three to ten times higher than populations of pregnant women who were sampled during a similar time frame from other cities and countries[64–66] and similar to levels observed in US-born pregnant women residing in California.[14, 27] These elevated levels are likely an unintended consequence of California's unique furniture flammability standard, which historically resulted in higher usage of chemical flame retardants there.[67] In contrast, concentrations of PFASs and PCBs in the MAMAS cohort were similar to or lower than serum concentrations in other contemporary populations of pregnant women.[65, 66, 68] Future work by our research group will examine socio-demographic determinants of EDC exposure in this study population.

We observed consistent, positive associations between individual PBDEs, their summary measure (ΣPBDEs) and OH-PBDEs (6-OHBDE-47) with plasma concentrations of IL-6 and TNF-α. We also observed negative associations between 5-OHBDE-47 and concentrations of IL-10. These results support previous reports from animal and *in vitro* studies that demonstrate individual PBDEs and their mixtures can shift cytokine production to a more pro-inflammatory phenotype (e.g., increased production of pro-inflammatory cytokines and/or decreased production of anti-inflammatory cytokines).[36, 37, 39, 69] Few prior epidemiologic studies have examined associations between serum PBDE concentrations and inflammation biomarkers, and results to date have been equivocal. In a cross-sectional of the US general population, Yuan et al. found significant positive associations between BDE-153 and two biomarkers of systemic inflammation, alkaline phosphatase and absolute neutrophil count.[39] However, associations with all other PBDE congeners were null as well associations with levels of C-reactive protein. Another population-based cross-sectional study of elderly men and women from Sweden did not observe any associations between serum BDE-47 and a wide range of inflammatory markers, including TNF-α and IL-6.[70] However, there are several notable differences between our study and these prior studies. Our study included repeated measures of inflammation biomarkers, which help reduce misclassification. In addition to PBDE congeners, we also examined OH-PBDEs, which have greater potential to disrupt endocrine-mediated pathways[32] and cause oxidative stress than their parent compounds.[71, 72] Our study focused on pregnant women, who may be more vulnerable to the inflammatory effects of EDCs.[22, 73] Indeed, we observed stronger associations between PBDE exposure and TNF-α during pregnancy than postpartum.

We also found consistent, positive associations between serum concentrations of PFOA, PFOS, and ΣPFASs with plasma concentrations of IL-6. These results are aligned with previous studies that report immunomodulation in experimental animals exposed to PFOA and PFOS, including altered inflammatory responses, cytokine production, reduced lymphoid weights, and decreased antibody production.[38, 74, 75] However, several of the *in vitro* studies suggest that PFASs stimulate an anti-inflammatory response, characterized by reduced production of IL-6, TNF-α, and/or other pro-inflammatory cytokines.[38, 74] To our knowledge, this study is among the first to examine these associations in a human

epidemiologic study. Additional research is needed to further characterize the inflammatory potential of PFASs in humans at levels commonly found in the environment.

We applied two statistical approaches to assess the effects of co-occurring chemical exposures. Mutual adjustment for other chemical classes resulted in stronger associations of PBDEs and PFASs with IL-6, and of PBDEs with TNF-α. WQS regression showed a significant positive association of the chemical index with IL-6 during pregnancy, and identified PFNA and PFDeA as the strongest contributors. Future work would benefit from an exposome framework that considers the totality of environmental exposures across the life course including non-chemical stressors.[76, 77] For example, inflammation may be a biological response that reflects cumulative exposures to chemical and non-chemical stressors since chronic stress-related biological response can initiate a cascade of immune and neuroendocrine processes that leads to alterations in endothelial function, production of pro-inflammatory cytokines, and telomere regulation.[77, 78]

Serum concentrations of PCBs were not independently associated with inflammation biomarkers but PCB-138 contributed to the overall effect of the chemical mixture index with IL-6. PCB serum concentrations were generally low and few congeners were well detected in this study population. Experimental studies suggest that coplanar PCBs (i.e., PCB-77 and 126) can induce cellular inflammation;[79, 80] however, those PCBs were not examined in the present study. Our results are consistent with prior epidemiologic studies that have generally observed few positive associations between PCB exposures and inflammation biomarkers in populations with low-level exposures.[70, 81]

We observed no meaningful associations between individual or summary measures of chemicals and LTL. *In vitro* research suggests dioxins may bind to the aryl hydrocarbon receptor (AhR) and induce telomerase activity, which elongates LTL.[46] Several epidemiologic studies in adults report a positive association between LTL and PCB exposures, particularly dioxin-like PCBs with high AhR activity.[46, 52] In our study population, dioxin-like PCBs were rarely detected. Furthermore, because telomere length and telomerase vary by age,[82] there may be differential susceptibility to environmental influences of telomere regulation by life stage.

Our study population consists of predominantly non-white, low-income women who were obese or overweight prior to pregnancy. The generalizability of our results to women with normal BMI is unknown since obesity could mediate and/or modify the relationship between chemical exposures and inflammation and cellular aging biomarkers. EDCs that can disrupt hormonally-regulated metabolic processes may contribute to obesity; however, epidemiological evidence is still emerging.[83] Adipose tissue in obese individuals releases high levels of proinflammatory cytokines, including IL-6 and TNF-α, leading to the characterization of obesity as a low-grade systemic chronic inflammatory state.[84, 85] Moreover, obesity and EDC exposures can both increase oxidative stress,[86] which is a precursor to increased inflammation and telomere shortening.[40, 41]

To help clarify these complex relationships, we examined potential effect modification by obesity status. We found stronger associations between certain chemicals (PFDeA, BDE-47,

BDE-99, BDE-100, ΣPBDEs) and increased levels of pro-inflammatory biomarkers among obese compared to overweight women, which is consistent with a recent study that suggests obesity magnifies the harmful effects of EDCs.[86] However, we also observed a small, significant positive association between BDE-153 and LTL among obese women only. This finding is difficult to interpret since obesity is typically associated with shorter telomeres.[87, 88] Future longitudinal studies are required to further characterize the complex relationship between EDC exposure, obesity, and inflammation as well as telomere length.

The implications of these findings for the health of pregnant women and their offspring are unclear and warrant further research. Inflammation during pregnancy may increase disease susceptibility in both women and their offspring with long-term consequences for physical and mental health for both the mother and her child.[89] Increased levels of pro-inflammatory cytokines and decreased amounts of anti-inflammatory cytokines during pregnancy are associated with a range of adverse pregnancy outcomes including preeclampsia, premature labor, and fetal growth restriction,[73, 89, 90] and may also influence the developing fetal brain.[91, 92] Increased inflammation during pregnancy and postpartum may also contribute to postpartum depression.[93, 94]

Limitations of this study include the modest sample size, which may reduce our ability to observe associations. Participants in this analysis underwent a mindful eating intervention, which may reduce generalizability. Chemical measurements were not available in follow-up visits, precluding our ability to measure changes in EDC exposure over pregnancy and postpartum. Thus, there may be measurement error in our exposure measures. Data on breastfeeding were not available; this may further contribute to measurement error as breastfeeding reduces the maternal body burden of EDCs in the postpartum period.[95] However, prior studies have found serum concentrations of persistent organic pollutants to be strongly correlated across pregnancy and postpartum period.[65, 96–98]

There are several notable strengths to our study. This study is among the first to investigate the relationship between exposure to persistent EDCs and biomarkers of inflammation and cellular aging, particularly during pregnancy and postpartum. While associations between these biological endpoints and other environmental exposures have been studied, this analysis is among the first to examine associations between PBDEs, PCBs, and PFASs and these biomarkers of inflammation and cellular aging in a human population. The repeated measurement data for the outcome biomarkers is an additional strength of the study as it reduces outcome misclassification. A third strength of this research is the investigation of fourteen EDCs representing four chemical classes and four outcome biomarkers representing diverse physiological processes, which provides granularity into the possible mechanisms of EDC exposure. These results further underscore the need to examine health effects of mixtures of EDCs in addition to examining one chemical at a time.

5. Conclusions

In conclusion, our findings suggest that exposures to certain persistent halogenated EDCs, such as PBDEs and PFASs, are associated with increased inflammation during pregnancy and the postpartum period. Future studies should confirm these relationships in larger

samples of racially and socioeconomically diverse pregnant and postpartum women across the range of BMI. Future studies should also investigate the implications of these associations on maternal and child health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Serum levels of PBDE congeners and their metabolites may increase inflammation in pregnant and postpartum women.
- Serum levels of PFAS chemicals may increase inflammation in pregnant and postpartum women.
- Obesity may exaggerate the effects of environmental chemicals on inflammation during pregnancy and postpartum.

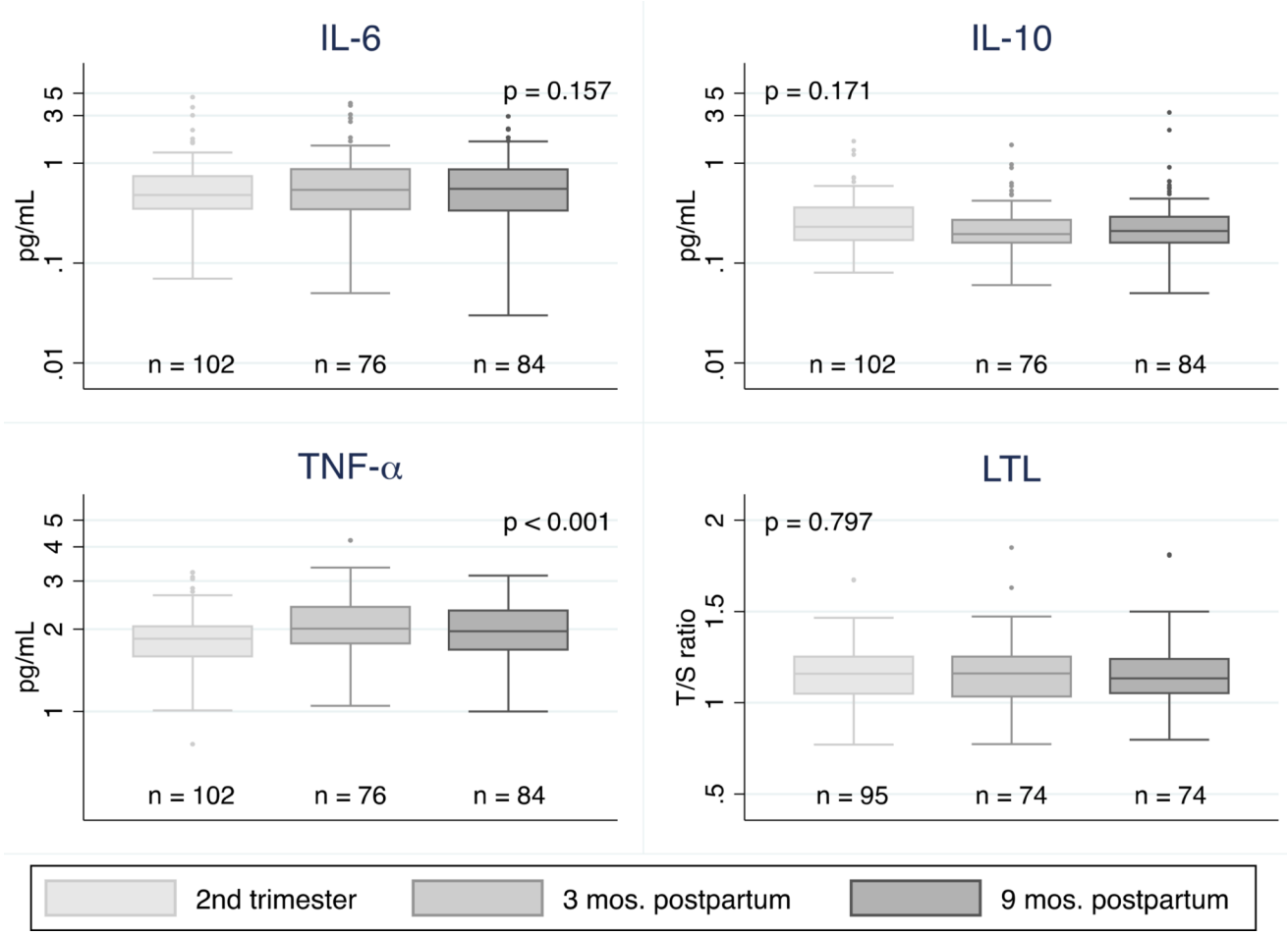

Figure 1. Boxplots of Biomarker Measurements by Visit

Distributions of outcome biomarker measurements by visit. The upper fence is calculated as 75th percentile + 1.5*IQR and the lower fence is calculated as 25th percentile – 1.5*IQR. P-values correspond to the global significance test for visit from unadjusted mixed effect linear models of outcome biomarkers on visit (modeled as a nominal categorical variable).

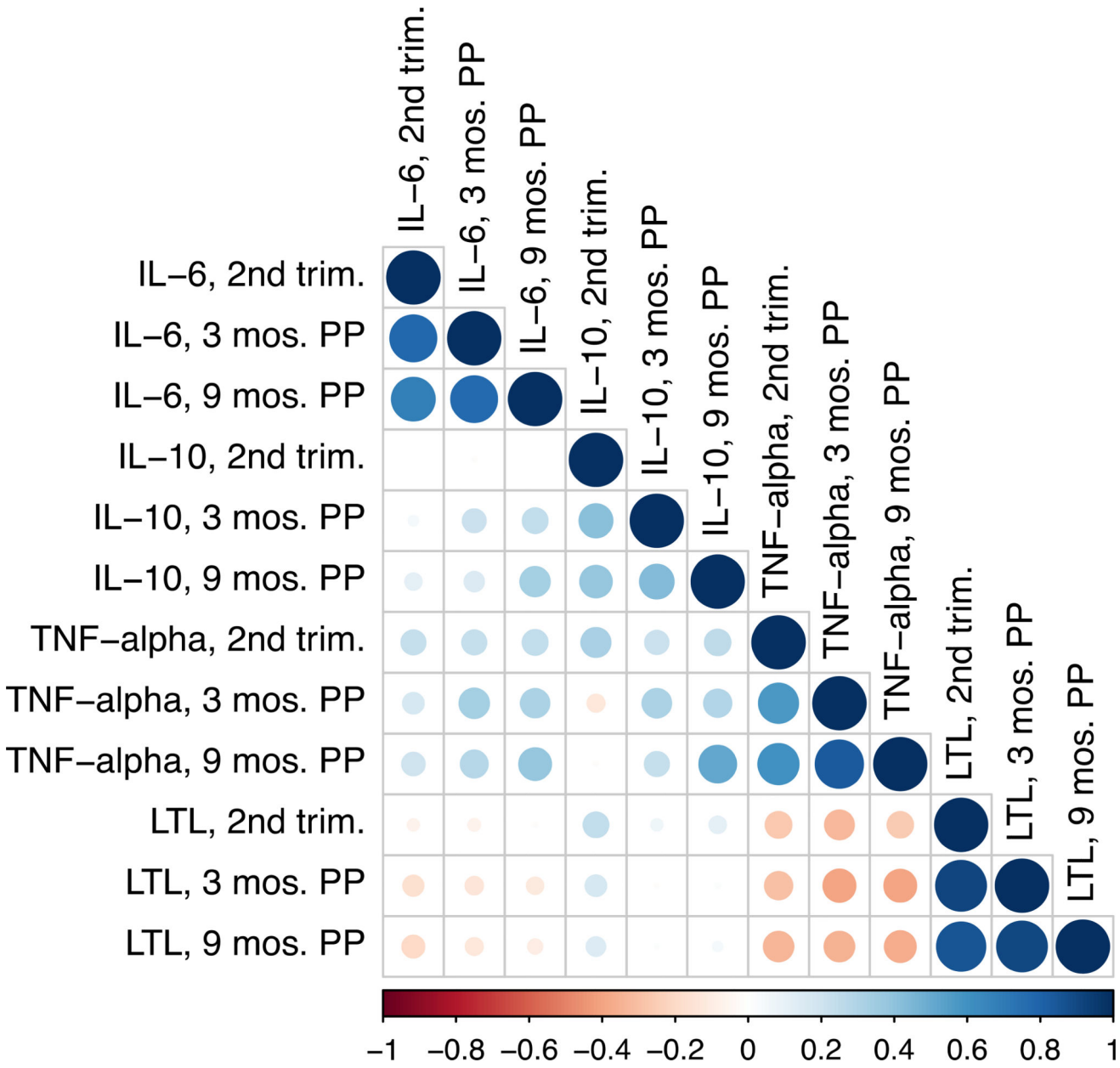

Figure 2.

Correlations within and between Outcome Biomarker Measurements over Time Spearman correlations between concentrations of IL-6, IL-10, TNF-α, and LTL measured during pregnancy (2nd trimester), three months postpartum, and nine months postpartum. Abbreviation: PP = postpartum.

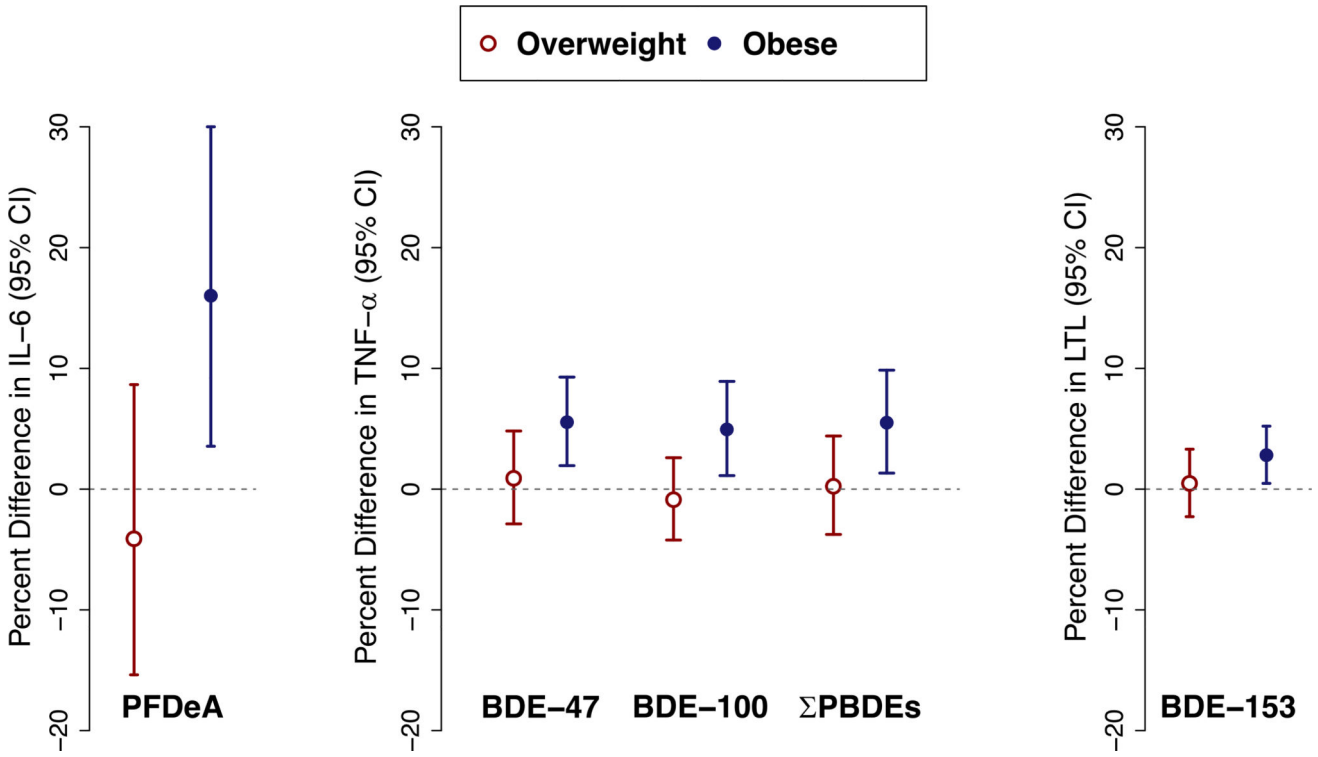

Figure 3. Percent Difference in Biomarker Measurements Associated with Serum EDC Concentrations, Stratified by Obesity

Percent difference in biomarker measurements associated with a doubling of serum EDC concentration. Estimates were obtained from mixed models adjusted for age, race/ethnicity, time-varying BMI, parity, education, smoking status, gestational weeks at baseline, visit, and obesity, with an interaction term for EDC concentration and obesity (BMI <30 [ref.] vs. BMI ≥30). Results shown are from models with a significant interaction of EDC concentration and obesity ($p<0.05$). Complete results from obesity interaction models can be found in Supplemental Materials, Tables S3–S6.

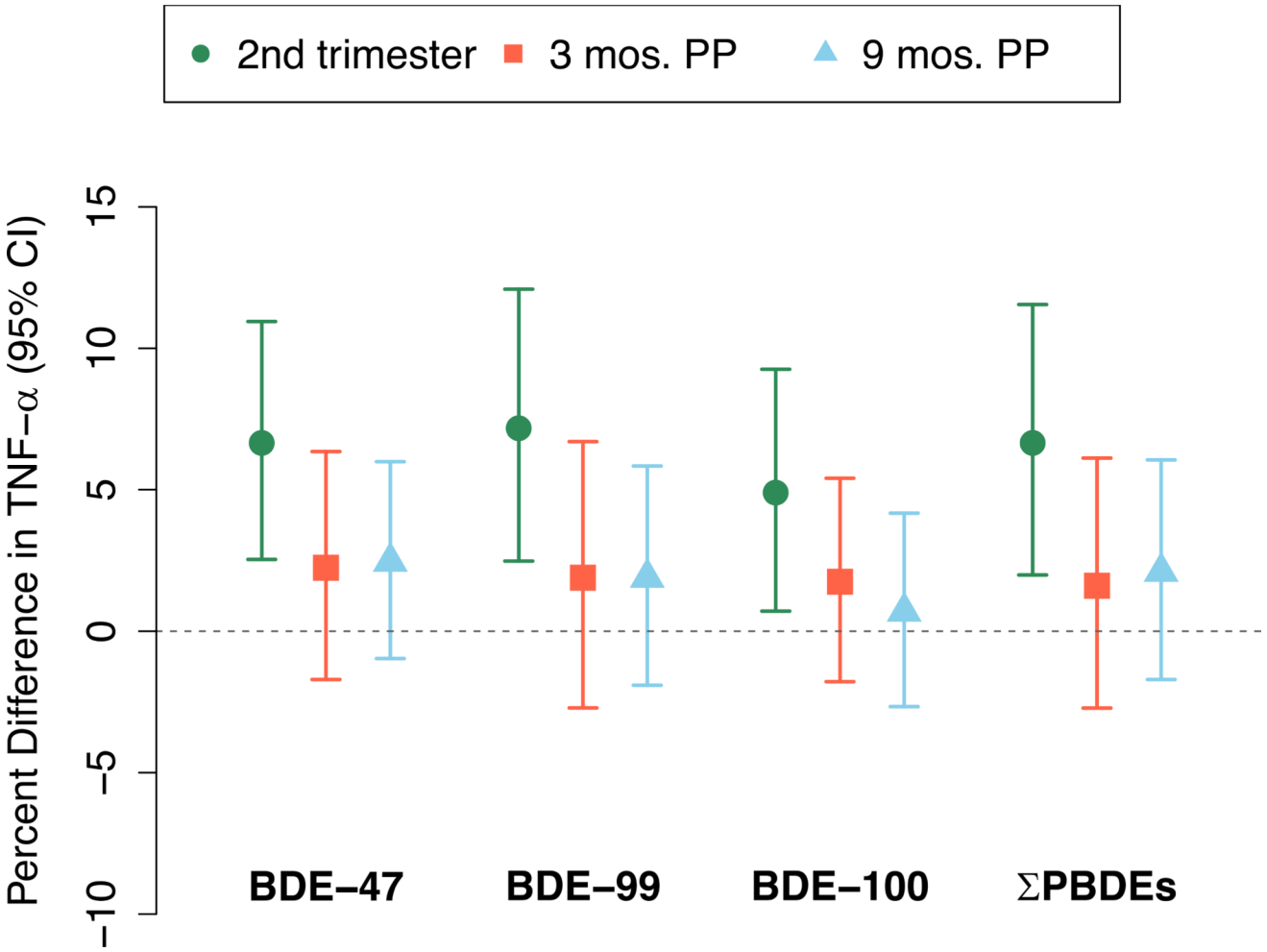

Figure 4.

Percent Difference in TNF-α Associated with Serum EDC Concentrations, Stratified by Visit Percent difference in TNF-α associated with a doubling of serum EDC concentration. Estimates were obtained from mixed models adjusted for age, race/ethnicity, time-varying BMI, parity, education, smoking status, gestational weeks at baseline, and visit, with interaction terms for EDC concentration and visit (2^{nd} trimester [ref.], 3 months postpartum, or 9 months postpartum). Visit was modeled using nominal categorical variables. Results are shown from models with a significant interaction of EDC concentration and visit ($p<0.05$). Results from cross-sectional models of all EDC-biomarker associations can be found in Supplemental Materials, Tables S7–S10.

Abbreviations: PP = postpartum.

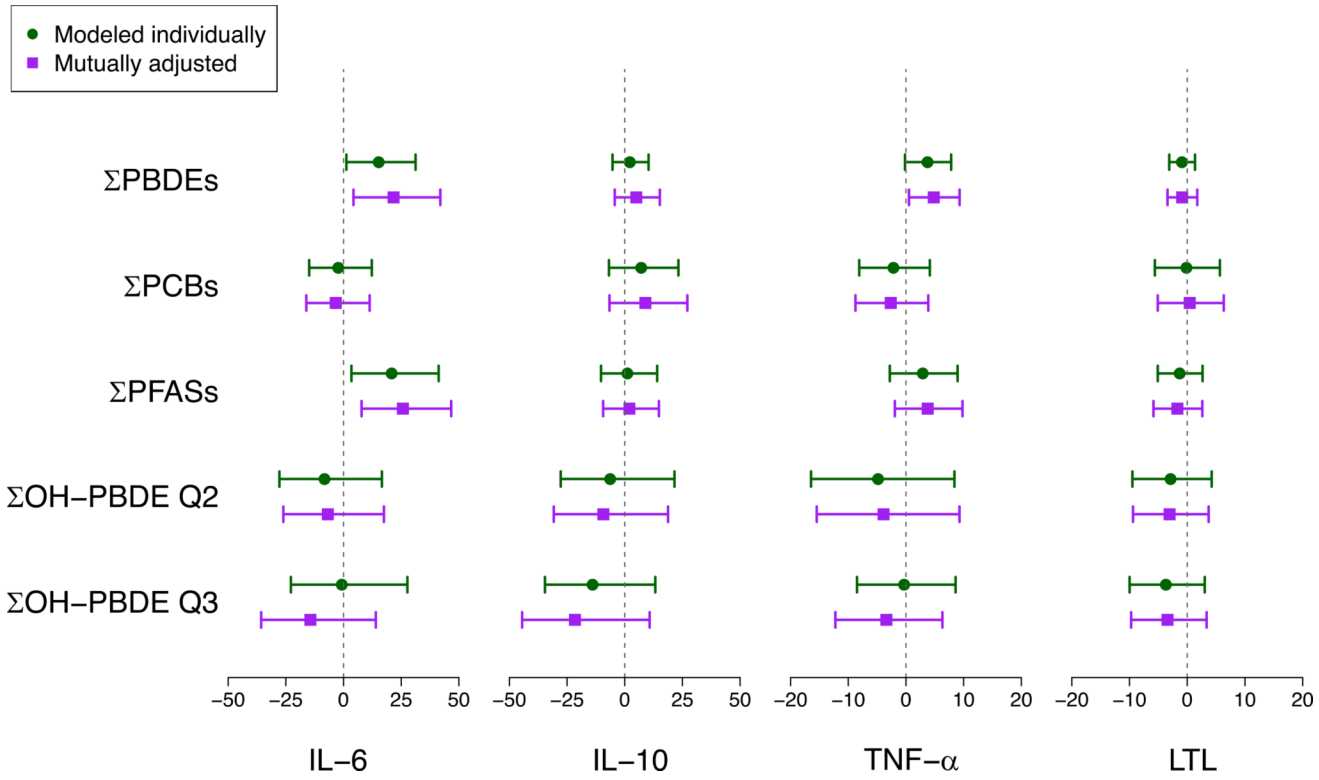

Figure 5. Percent Difference in Biomarker Measurements Associated with Chemical Class Sums, Modeled Individually and Mutually Adjusted for Other Chemical Class Sums

Percent difference in biomarker measurements associated with chemical class sums, modeled individually and adjusted for the category sums of other EDC classes. In models where exposure is modeled continuously (e.g. ΣPBDEs), percent difference estimates are for a doubling of EDC concentration. In models where exposure is modeled as tertiles (ΣOH-PBDEs), percent difference is relative to the referent group. All models were adjusted for age, race/ethnicity, time-varying BMI, parity, education, smoking status, gestational weeks at baseline, and visit.

Table 1

Descriptive Statistics for Serum Concentrations of EDCs at Baseline (2nd Trimester) Visit

Chemical	MDL	% > MDL	GM (GSD)	50th percentile	95th percentile
Polybrominated diphenyl ethers (PBDEs) (ng/g lipid)					
BDE-47	0.05	100	32.93 (2.28)	28.8	129.58
BDE-99	0.03	89	8.42 (2.11)	7.44	25.22
BDE-100	0.01	81	4.92 (2.50)	5.07	31.09
BDE-153	0.01	91	8.62 (2.52)	8.62	40.22
ΣPBDEs	--	--	58.38 (2.15)	49.01	227.23
Polychlorinated biphenyls (PCBs) (ng/g lipid)					
PCB-138	0.01	57	2.20 (2.56)	2.82	11.15
PCB-153	0.01	87	3.95 (1.88)	4.13	11.11
PCB-180	0.01	57	1.98 (2.40)	1.68	8.01
ΣPCBs	--	--	8.89 (1.95)	9.59	31.26
Perfluoroalkyl substances (PFASs) (ng/mL)					
Perfluorooctane sulfonate (PFOS)	0.267	100	2.90 (1.75)	2.83	6.65
Perfluorooctanoic acid (PFOA)	0.052	98	1.21 (2.08)	1.40	2.46
Perfluorohexane sulfonate (PFHxS)	0.038	99	0.53 (2.19)	0.50	2.35
Perfluorononanoic acid (PFNA)	0.074	100	0.58 (1.68)	0.57	1.15
Perfluorodecanoic acid (PFDeA)	0.115	70	0.18 (2.19)	0.18	0.67
ΣPFASs	--	--	5.87 (1.58)	6.11	11.55
Hydroxylated polybrominated diphenyl ethers (OH-PBDEs) (ng/mL)					
5-OHBDE-47	0.003	50	0.003 (7.52)	0.004	0.07
6-OHBDE-47	0.003	55	0.004 (4.96)	0.005	0.05
ΣOH-PBDEs	--	--	0.01 (4.38)	0.01	0.08

Abbreviations: MDL = method detection limit; GM = geometric mean; GSD = geometric standard deviation

Table 2

Outcome Biomarkers at Baseline (2nd Trimester) by Demographic Characteristics

		Geometric Mean (GSD)			
	n (%)	**IL-6 (pg/mL) (n=102)**	**IL-10 (pg/mL) (n=102)**	**TNF-α (pg/mL) (n=102)**	**LTL (T/S ratio) (n=95)**
All participants	103 (100.0)	0.50 (2.01)	0.25 (1.78)	1.83 (1.29)	1.14 (1.16)
Maternal age (years)					
18–25	35 (34.0)	0.50 (1.81)	0.27 (1.68)[a]	1.82 (1.25)	1.19 (1.15)
26–30	36 (35.0)	0.56 (2.18)	0.29 (1.95)	1.85 (1.34)	1.15 (1.14)
31–42	32 (31.1)	0.44 (2.03)	0.19 (1.55)	1.81 (1.29)	1.09 (1.17)
Race/ethnicity					
White	14 (13.7)	0.44 (1.74)[a]	0.25 (1.66)	1.89 (1.15)	1.14 (1.18)
African American	35 (34.3)	0.64 (2.30)	0.23 (1.67)	1.81 (1.30)	1.12 (1.12)
Latina	33 (32.4)	0.52 (1.64)	0.27 (1.88)	1.80 (1.36)	1.18 (1.16)
Other/Multiracial	20 (19.6)	0.35 (2.02)	0.25 (1.93)	1.91 (1.25)	1.16 (1.16)
BMI (kg/m^2) at baseline					
< 30 (range 23.7, 29.9)	43 (41.8)	0.41 (1.75)[a]	0.25 (1.67)	1.77 (1.25)	1.15 (1.18)
≥ 30 (range 30.0, 42.8)	60 (58.3)	0.58 (2.12)	0.25 (1.87)	1.88 (1.32)	1.14 (1.14)
Education					
≤ HS	10 (9.7)	0.43 (1.90)	0.29 (1.95)	1.86 (1.22)	1.16 (1.14)
HS graduate	27 (26.2)	0.57 (1.76)	0.25 (1.61)	1.84 (1.35)	1.12 (1.12)
Some college	52 (50.5)	0.53 (2.14)	0.25 (1.87)	1.85 (1.30)	1.17 (1.14)
≥ College graduate	14 (13.6)	0.35 (1.91)	0.22 (1.72)	1.74 (1.19)	1.09 (1.25)
Marital status					
Married or in a committed relationship	69 (67.0)	0.46 (1.96)[a]	0.24 (1.76)	1.86 (1.25)	1.14 (1.15)
Other	34 (33.0)	0.62 (2.05)	0.26 (1.82)	1.77 (1.37)	1.16 (1.16)
Income					
≤ Federal poverty level	44 (45.4)	0.59 (2.17)[a]	0.26 (1.91)	1.83 (1.33)	1.13 (1.15)
> Federal poverty level	53 (54.6)	0.44 (1.87)	0.24 (1.70)	1.85 (1.25)	1.14 (1.15)
Gestational age at baseline (weeks)					

		Geometric Mean (GSD)			
	n (%)	**IL-6 (pg/mL) (n=102)**	**IL-10 (pg/mL) (n=102)**	**TNF-α (pg/mL) (n=102)**	**LTL (T/S ratio) (n=95)**
< 14 (range 10.4, 13.9)	27 (26.2)	0.45 (1.62)	0.24 (1.65)	1.74 (1.24)	1.16 (1.13)
14–17	36 (35.0)	0.49 (2.38)	0.27 (1.74)	1.84 (1.38)	1.12 (1.18)
> 17 (range 17.1, 24.1)	40 (38.8)	0.55 (1.91)	0.24 (1.91)	1.89 (1.24)	1.16 (1.15)
Parity					
0	50 (48.5)	0.48 (1.83)	0.28 (1.93)	1.91 (1.32)	1.16 (1.16)
≥ 1	53 (51.5)	0.52 (2.18)	0.22 (1.59)	1.76 (1.26)	1.13 (1.15)
Smoking status					
Current	5 (5.2)	0.55 (1.57)	0.32 (2.83)	1.78 (1.37)	1.19 (1.19)
Former	42 (43.3)	0.41 (1.90)	0.25 (1.66)	1.84 (1.25)	1.17 (1.14)
Never	50 (51.6)	0.57 (2.04)	0.25 (1.83)	1.85 (1.32)	1.13 (1.17)

Abbreviations: IL-6 = interleukin 6; IL-10 = interleukin 10; TNF-α = tumor necrosis factor alpha; LTL = leukocyte telomere length; BMI = body mass index; HS = high school

Note: Some percentages do not add up to 100.0 due to rounding.

[a] $p < 0.05$.

Table 3

Percent Difference in Biomarker Measurements Associated with Serum EDC Concentrations: Repeated-Measures Analysis

	Percent difference (95% CI)[a, b]			
	IL-6	**IL-10**	**TNF-α**	**LTL**
PBDEs (ng/g lipid)				
BDE-47	12.22 (−0.73, 26.85)	1.09 (−6.01, 8.72)	4.00 (0.52, 7.61)[e]	−1.42 (−3.58, 0.79)
BDE-99	14.87 (0.45, 31.36)[e]	2.56 (−5.12, 10.86)	3.95 (−0.08, 8.14)	−0.97 (−3.30, 1.42)
BDE-100	9.37 (−1.10, 20.95)	−2.21 (−8.91, 4.99)	2.64 (−0.79, 6.18)	−1.09 (−2.78, 0.63)
BDE-153	12.68 (3.31, 22.90)[e]	3.26 (−4.42, 11.55)	0.65 (−2.92, 4.34)	1.72 (−0.52, 4.01)
ΣPBDEs	15.26 (1.24, 31.22)[e]	2.23 (−5.29, 10.35)	3.74 (−0.19, 7.82)	−0.91 (−3.12, 1.35)
PCBs (ng/g lipid)				
PCB-153	−3.92 (−16.02, 9.91)	13.36 (−0.20, 28.78)	−1.93 (−7.07, 3.50)	0.85 (−4.16, 6.11)
PCB-138 Q1[c] (ref)	--	--	--	--
PCB-138 Q2	16.87 (−15.08, 60.84)	−1.35 (−20.51, 22.43)	−3.32 (−14.59, 9.43)	−3.79 (−11.27, 4.33)
PCB-138 Q3	8.11 (−20.12, 46.33)	10.89 (−16.71, 47.64)	3.76 (−6.77, 15.49)	−3.16 (−11.39, 5.83)
p trend	0.49	0.55	0.72	0.41
PCB-180 Q1[c] (ref)	--	--	--	--
PCB-180 Q2	−3.24 (−30.97, 35.62)	−8.27 (−28.73, 18.06)	−8.08 (−19.32, 4.73)	−2.19 (−10.96, 7.44)
PCB-180 Q3	−12.85 (−38.79, 24.09)	−0.77 (−27.52, 35.85)	−2.45 (−15.48, 12.59)	1.36 (−8.58, 12.39)
p trend	0.51	0.82	0.51	0.94
ΣPCBs	−2.25 (−14.86, 12.23)	7.14 (−6.85, 23.23)	−2.17 (−8.09, 4.13)	−0.13 (−5.60, 5.66)
PFASs (ng/mL)				
PFOS	14.58 (1.37, 29.51)[e]	4.09 (−7.19, 16.75)	3.33 (−1.51, 8.41)	−0.72 (−3.86, 2.53)
PFOA	9.88 (1.65, 18.79)[e]	−2.82 (−9.77, 4.67)	0.11 (−3.37, 3.71)	−0.41 (−3.15, 2.42)
PFHxS	5.38 (−3.77, 15.39)	−4.14 (−11.70, 4.06)	0.79 (−2.74, 4.44)	−0.00 (−2.42, 2.47)
PFNA	11.78 (−2.73, 28.47)	−2.49 (−12.45, 8.60)	−1.06 (−5.61, 3.71)	−1.45 (−5.16, 2.40)
PFDeA	5.81 (−3.30, 15.78)	−0.96 (−9.37, 8.24)	−3.13 (−6.24, 0.09)	1.08 (−1.21, 3.42)
ΣPFASs	20.87 (3.46, 41.22)[e]	1.16 (−10.27, 14.05)	2.91 (−2.80, 8.95)	−1.30 (−5.11, 2.66)
OH-PBDEs (ng/mL)				
5-OHBDE-47 Q1[c] (ref)	--	--	--	--
5-OHBDE-47 Q2	7.59 (−14.87, 35.99)	−8.44 (−28.28, 16.89)	−10.37 (−20.49, 1.04)	−3.84 (−9.89, 2.63)
5-OHBDE-47 Q3	−5.44 (−32.32, 32.14)	−25.81 (−38.64, −10.29)[e]	1.35 (−6.98, 10.41)	−4.71 (−11.77, 2.93)
p trend	1.00	0.02	0.34	0.15
6-OHBDE-47 Q1[c] (ref)	--	--	--	--
6-OHBDE-47 Q2	−9.60 (−30.90, 18.27)	10.05 (−11.75, 37.22)	4.33 (−6.87, 16.88)	1.52 (−4.89, 8.36)
6-OHBDE-47 Q3	51.06 (15.45, 97.66)[e]	2.52 (−20.56, 32.30)	8.78 (−1.20, 19.77)	−0.83 (−6.97, 5.71)
p trend	0.02	0.69	0.10	0.95
ΣOH-PBDEs Q1[d] (ref)	--	--	--	--
ΣOH-PBDEs Q2	−8.22 (−27.77, 16.63)	−6.29 (−27.74, 21.52)	−4.84 (−16.46, 8.39)	−2.88 (−9.51, 4.23)

	Percent difference (95% CI)[a, b]			
	IL-6	**IL-10**	**TNF-α**	**LTL**
ΣOH-PBDEs Q3	−0.73 (−22.82, 27.70)	−13.92 (−34.56, 13.25)	−0.32 (−8.50, 8.60)	−3.69 (−9.99, 3.04)
p trend	0.85	0.31	0.79	0.26

[a] In models where exposure is modeled continuously, percent difference estimates are for a doubling of EDC concentration. In models where exposure is modeled as tertiles, percent difference is relative to the referent group.

[b] Adjusted for age, race/ethnicity, time-varying BMI, parity, education, smoking status, gestational weeks at baseline, and visit.

[c] Q1 = below MDL; Q2 = at or below 50th percentile of values above MDL; Q3 = above 50th percentile of values above MDL.

[d] Q1 = both values below MDL; Q2 = sum of values at or below 50th percentile; Q3 = sum of values above 50th percentile.

[e] $p < 0.05$.