Environment International 115 (2018) 9–20

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

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

Ami R. Zota[a,*], Ruth J. Geller[a], Laura E. Romano[a], Kimberly Coleman-Phox[b], Nancy E. Adler[c], Emily Parry[d], Miaomiao Wang[d], June-Soo Park[d], Angelo F. Elmi[a], Barbara A. Laraia[e], Elissa S. Epel[c]

[a] Milken Institute School of Public Health, The George Washington University, Washington, DC, USA
[b] Center for Health and Community, School of Medicine, University of California, San Francisco, CA, USA
[c] Department of Psychiatry, School of Medicine, University of California, San Francisco, CA, USA
[d] Environmental Chemistry Laboratory, California Department of Toxic Substances Control, Berkeley, CA, USA
[e] Division of Community Health and Human Development, School of Public Health, University of California, Berkeley, CA, USA

ARTICLE INFO

Handling Editor: Heather Stapleton

Keywords:
Polybrominated diphenyl ethers
Per- and polyfluorochemicals
Leukocyte telomere length
Obesity
Environmental chemicals
Prenatal exposures

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 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 pro-inflammatory 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 to 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.

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

* Corresponding author at: Department of Environmental and Occupational Health, Milken Institute School of Public Health, The George Washington University, 950 New Hampshire Avenue NW, Washington, DC 20052, USA.
E-mail address: azota@gwu.edu (A.R. Zota).

https://doi.org/10.1016/j.envint.2018.02.044
Received 17 October 2017; Received in revised form 31 January 2018; Accepted 25 February 2018
Available online 10 March 2018
0160-4120/

exposure (Mitro et al., 2015; Centers for Disease Control and Prevention (CDC), 2009). PBDEs were used as flame retardants in upholstered furniture, electronics, and textiles until they were phased out of use in the US around 2004 (US Environmental Protection Agency (US EPA), 2014). PCBs were once widely used as lubricants and coolants, and now persist in the environment despite being banned in 1979 (Agency for Toxic Substances and Disease Registry (ATSDR), 2000). PFASs are used to impart water and stain resistance to products such as upholstery, non-stick cookware, and food packaging (US EPA, 2017). 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 (Pan et al., 2017). All three chemical classes have long elimination half-lives in the body (Geyer et al., 2004; Ritter et al., 2011; Olsen et al., 2007); may persist in the indoor environment (Mitro et al., 2016a; Harrad and Diamond, 2006); and can biomagnify in the food web (Haukas et al., 2007). PBDEs and PCBs are lipophilic while PFASs preferentially bind to proteins such as albumin (Beesoon and Martin, 2015). Among US populations, serum concentrations of PCBs declined after their phase-out but have plateaued in recent years (Zota et al., 2013; Tee et al., 2003). Exposures to PBDEs and PFASs have also declined after their market phase-out (Zota et al., 2013; Olsen et al., 2017). Nevertheless, these chemicals are routinely detected in pregnant and lactating women (Mitro et al., 2015; Morello-Frosch et al., 2016; Woodruff et al., 2011).

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 (Boas et al., 2012; Diamanti-Kandarakis et al., 2009). For both women and their offspring, pregnancy and early postnatal life represent vulnerable periods for high sensitivity to EDC exposures (Diamanti-Kandarakis et al., 2009; Gore et al., 2015; A. Leung et al., 2016; Moya et al., 2014). Indeed, higher levels of EDCs during pregnancy have been associated with changes in thyroid hormone levels in pregnant women (Vuong et al., 2015; Abdelouahab et al., 2013; Berg et al., 2017; Zota et al., 2011), as well as adverse birth outcomes, and neurodevelopmental harm in their offspring (Johnson et al., 2014; Lam et al., 2017).

EDCs may also increase disease risks through induction of oxidative stress and inflammation (Johnson et al., 2013; Wiegers and Reul, 1998). PBDEs and OH-PBDEs show antagonistic activity towards the glucocorticoid receptor (Kojima et al., 2009; H. Liu et al., 2015), which can promote chronic inflammation (Zhang et al., 2016; Yang et al., 2016). 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 (Park et al., 2014; Park and Loch-Caruso, 2014). 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 (DeWitt et al., 2012). In a cross-sectional study of the US general population, exposures to certain PBDE congeners were positively associated with some inflammation biomarkers (Yuan et al., 2017).

Oxidative stress and inflammation can also influence regulation of telomeres (O'Donovan et al., 2011; Oikawa and Kawanishi, 1999), non-coding segments of DNA found at the ends of chromosomes that may be a novel biomarker of EDC toxicity (Calado and Young, 2009). 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 (Calado and Young, 2009; Cong et al., 2002). Although telomeres typically shorten over the life of a cell, under certain circumstances telomeres can elongate (Cong et al., 2002). Leukocyte telomere length (LTL) in blood is commonly measured in epidemiological studies (Haycock et al., 2014; Willeit et al., 2014; Mitro et al., 2016b). Exposure to some environmental chemicals may influence LTL, with both positive and inverse associations reported in the literature (Guzzardi et al., 2016; Hou et al., 2012; Zhang et al., 2013; Zota et al., 2015). For example, several cross-sectional studies have found an association between serum concentrations of PCBs and longer LTL in adults (Mitro et al., 2016b; Callahan et al., 2017; Shin et al., 2010).

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 excess weight gain during pregnancy. The intervention was registered at clinicaltrials.gov as NCT01307683. Recruitment and retention methods have been previously described (Coleman-Phox et al., 2013). 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 and 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 (Fig. 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 min, and then placed on ice. Samples were centrifuged at 1300*g* for 10 min 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 1300*g* for 10 min 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. 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 (Wang et al., 2011). 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 are described in detail elsewhere (Zota et al., 2011). 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 (Phillips et al., 1989).

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 (Zota et al., 2011; Baccarelli et al., 2005; Helsel, 1990). 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 SDs 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) (Lin et al., 2010). Methods for the analysis of LTL in the MAMAS cohort has been described in detail elsewhere (C. Leung et al., 2016).

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) 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 (Tukey, 1977). 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 $(\exp[\ln 2 \times (\beta \pm 1.96 \times SE)] - 1) \times 100\%$ (Zota et al., 2016). For EDCs modeled as categorical variables, percent difference in IL-6, IL-10, TNF-α, and LTL comparing an EDC concentration to the referent

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.

category (below MDL) was calculated as $(\exp(\beta) - 1) \times 100\%$, with the 95% CIs estimated as $(\exp(\beta \pm 1.96 \times SE) - 1) \times 100\%$ (Zota et al., 2016). Additionally, for chemicals modeled as categorical variables, a linear test for trend was performed by modeling the median chemical concentration of each tertile as a continuous term. In cross-sectional models, the percent difference and 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 (Carrico et al., 2014) 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 (Rubin, 1987). (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

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

Table 2
Outcome biomarkers at baseline (2nd trimester) by demographic characteristics.

	n (%)	Geometric mean (GSD)			
		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)					
< 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] $p < 0.05$.

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 (Fig. 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 (Fig. 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 $p < 0.05$).

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% (95% CI 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

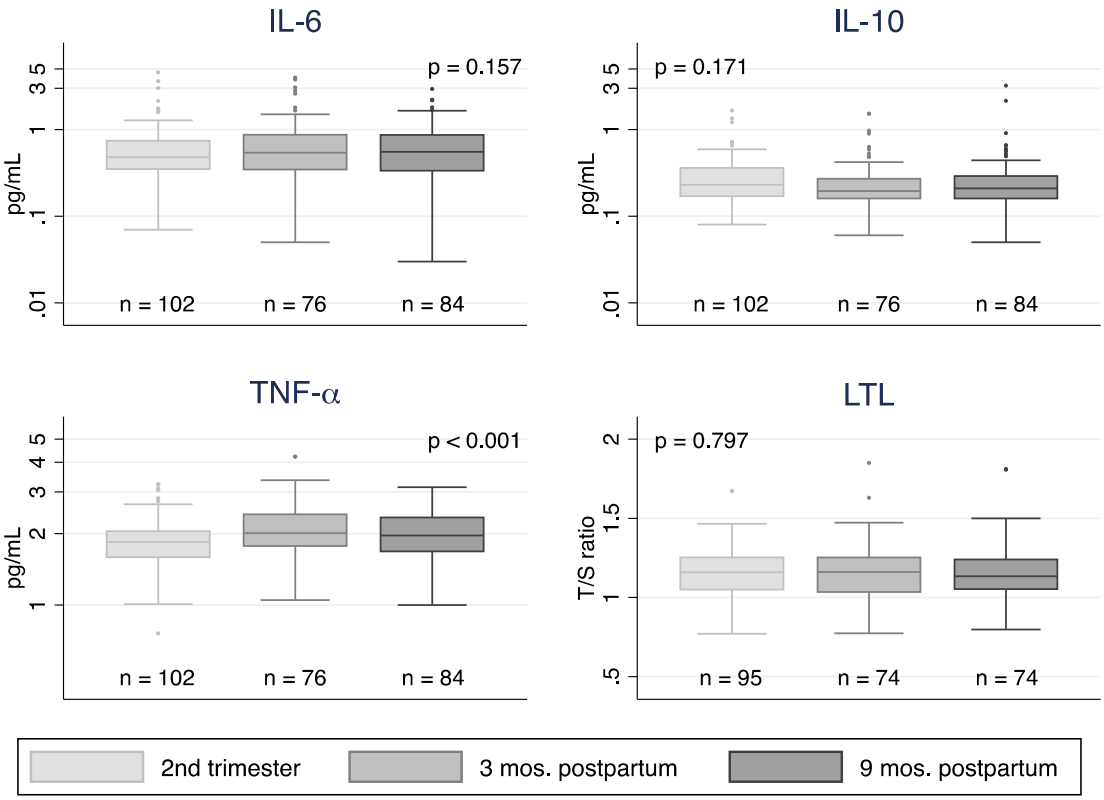

Fig. 1. Boxplots of biomarker measurements by visit. The upper fence is calculated as 75th percentile + 1.5 * IQR and the lower fence is calculated as 25th percentile − 1.5 * IQR. The p-values correspond to the global significance test for visit from unadjusted mixed effect linear models of outcome biomarkers on visit (modeled as a nominal categorical variable).

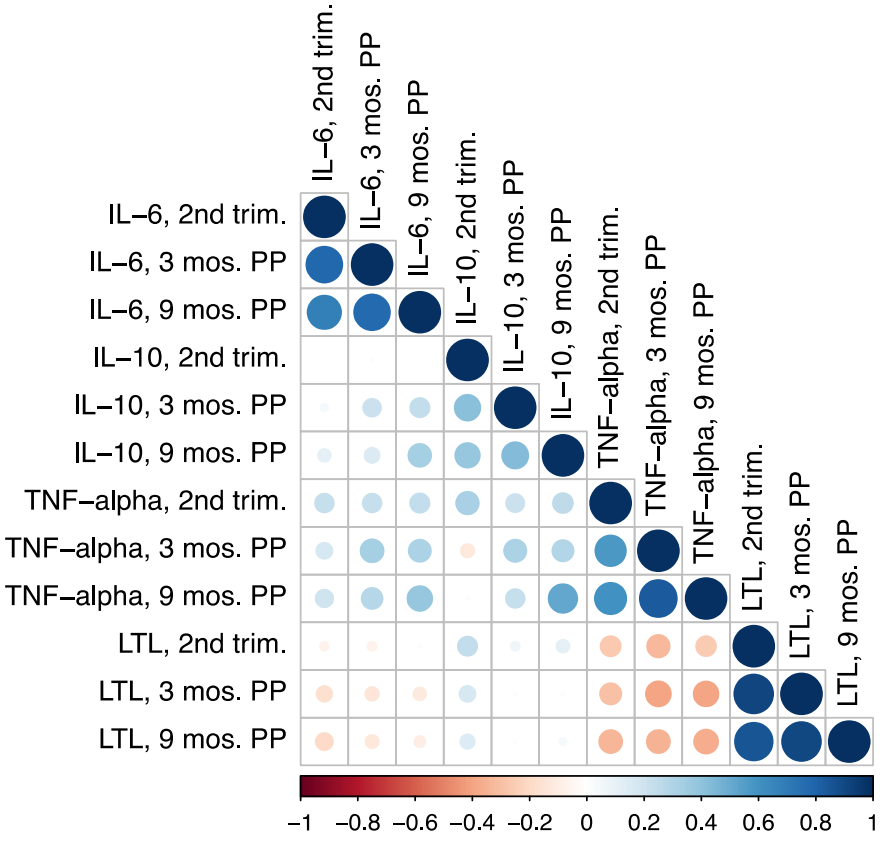

Fig. 2. Correlations within and between outcome biomarker measurements over time. Spearman correlations between concentrations of IL-6, IL-10, TNF-α, and LTL measured during pregnancy (2nd trimester), three months postpartum, and nine months postpartum. Abbreviation: PP = postpartum.

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)
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] $p < 0.05$.

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 (Fig. 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 materials). 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 nine 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 (Fig. 4).

Adjustment for the sums of other EDC classes resulted in meaningful differences for multiple chemical-biomarker associations (Fig. 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

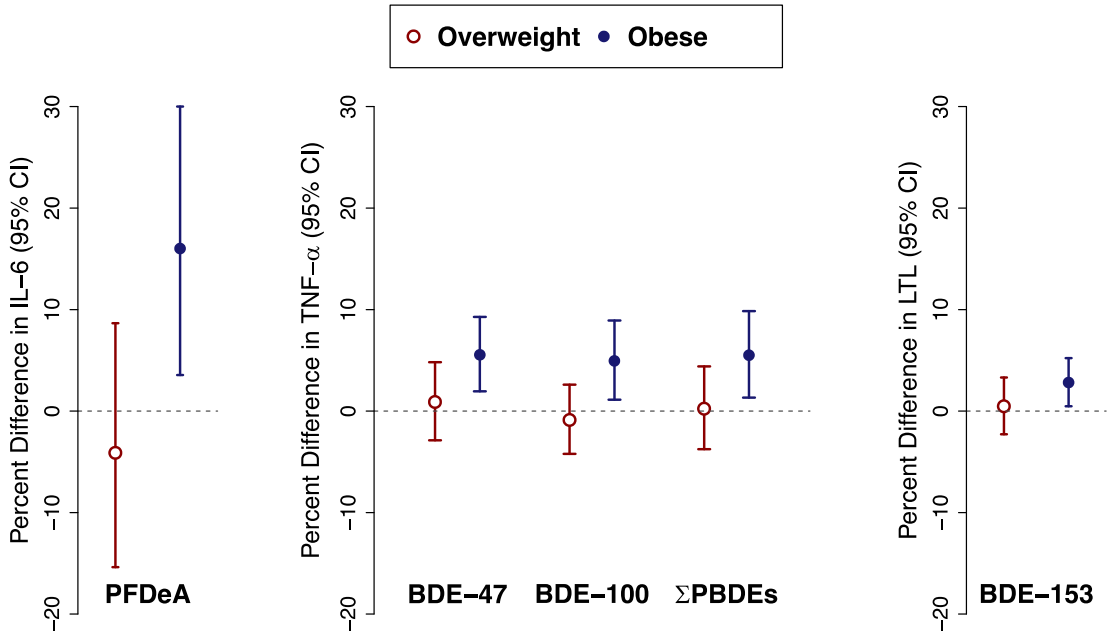

Fig. 3. Percent difference in biomarker measurements associated with a doubling of serum EDC concentrations, stratified by obesity. Estimates were obtained from mixed models adjusted for age, race/ethnicity, time-varying BMI, parity, education, smoking status, gestational weeks at baseline, visit, and 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.

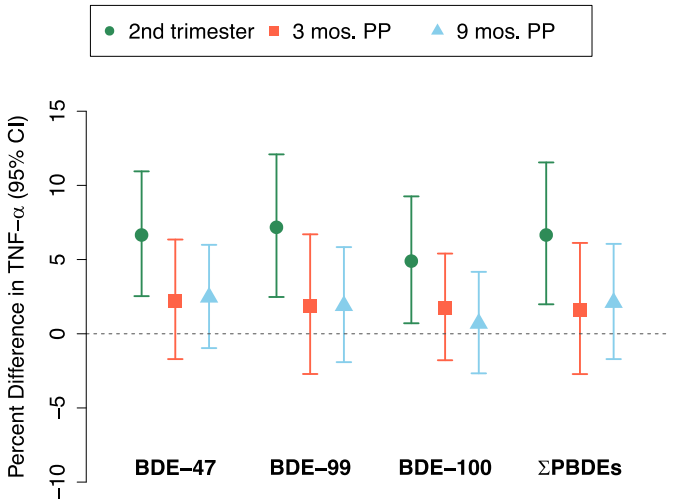

Fig. 4. Percent difference in TNF-α associated with a doubling of serum EDC concentrations, stratified by visit. Estimates were obtained from mixed models adjusted for age, race/ethnicity, time-varying BMI, parity, education, smoking status, gestational weeks at baseline, and visit, with interaction terms for EDC concentration and visit (2nd 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.

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 (Supplemental materials, Fig. 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.

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 materials, 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 materials, Table S13). Multiple imputation for missing values of smoking did not qualitatively change results (Supplemental materials, 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

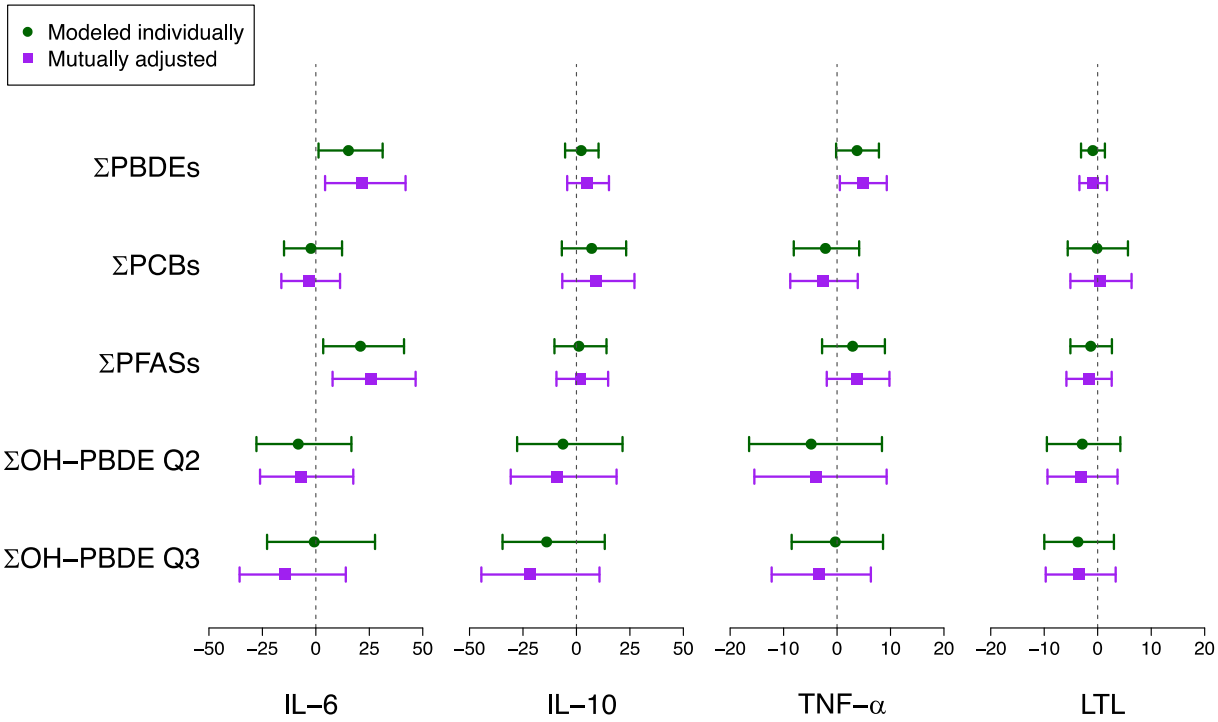

Fig. 5. Percent difference in biomarker measurements associated with chemical class sums, modeled individually and mutually adjusted for other chemical class sums. In models where exposure is modeled continuously (e.g. ΣPBDEs), percent difference estimates are for a doubling of EDC concentration. In 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.

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 (Butt et al., 2016; Fisher et al., 2016; Bjerregaard-Olesen et al., 2017a) and similar to levels observed in US-born pregnant women residing in California (Zota et al., 2013; Zota et al., 2011). 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 (Zota et al., 2008). 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 (Fisher et al., 2016; Bjerregaard-Olesen et al., 2017a; Bjerregaard-Olesen et al., 2017b). 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) (Park et al., 2014; Park and Loch-Caruso, 2014; Yuan et al., 2017; Peltier et al., 2012). 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 study 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 (Yuan et al., 2017). 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 (Kumar et al., 2014). 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 (Kojima et al., 2009) and cause oxidative stress than their parent compounds (Usenko et al., 2012; Usenko et al., 2011). Our study focused on pregnant women, who may be more vulnerable to the inflammatory effects of EDCs (A. Leung et al., 2016; Challis et al., 2009). 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 (DeWitt et al., 2012; Corsini et al., 2012; DeWitt et al., 2009). 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 (DeWitt et al., 2012; Corsini et al., 2012). 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 (Wild, 2012; Clougherty et al., 2014). 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 (Clougherty et al., 2014; Shalev et al., 2013).

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 (D. Liu et al., 2015; Hennig et al., 2002); 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 (Kumar et al., 2014; Turyk et al., 2015).

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 (Mitro et al., 2016b). Several epidemiologic studies in adults report a positive association between LTL and PCB exposures, particularly dioxin-like PCBs with high AhR activity (Mitro et al., 2016b; Shin et al., 2010). In our study population, dioxin-like PCBs were rarely detected. Furthermore, because telomere length and telomerase vary by age (Iwama et al., 1998), 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 (Heindel et al., 2015). Adipose tissue in obese individuals releases high levels of pro-inflammatory cytokines, including IL-6 and TNF-α, leading to the characterization of obesity as a low-grade systemic chronic inflammatory state (Bullo et al., 2007; Makki et al., 2013). Moreover, obesity and EDC exposures can both increase oxidative stress (Hu et al., 2017), which is a precursor to increased inflammation and telomere shortening (O'Donovan et al., 2011; Oikawa and Kawanishi, 1999).

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 (Hu et al., 2017). 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 (Muezzinler et al., 2014; Mundstock et al., 2015). 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 (Vohr et al., 2017). 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 pre-eclampsia, premature labor, and fetal growth restriction (Challis et al., 2009; Vohr et al., 2017; Romero et al., 2007), and may also influence the developing fetal brain (Graham et al., 2018; Smith et al., 2007). Increased inflammation during pregnancy and postpartum may also contribute to postpartum depression (Corwin et al., 2008; Corwin and Pajer, 2008).

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 (Glynn et al., 2012). However, prior studies have found serum concentrations of persistent organic pollutants to be strongly correlated across pregnancy and postpartum period (Fisher et al., 2016; Fei et al., 2007; Adetona et al., 2013; Daniels et al., 2010).

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.

Acknowledgements

The authors thank Susanna Mitro and Suril Mehta for their assistance with data management and data analysis and Greg Yeh and Wendy Duong for help with sample preparation. Research summarized in this publication was supported by the National Institutes of Health (NHLBI U01 HL097973 and NIEHS R00 ES019881). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Appendix A. Supplemental Materials

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.02.044.

References

Abdelouahab, N., Langlois, M.F., Lavoie, L., Corbin, F., Pasquier, J.C., Takser, L., 2013. Maternal and cord-blood thyroid hormone levels and exposure to polybrominated diphenyl ethers and polychlorinated biphenyls during early pregnancy. Am. J. Epidemiol. 178 (5), 701–713.

Adetona, O., Horton, K., Sjodin, A., Jones, R., Hall, D.B., Aguillar-Villalobos, M., Cassidy, B.E., Vena, J.E., Needham, L.L., Naeher, L.P., 2013. Concentrations of select persistent organic pollutants across pregnancy trimesters in maternal and in cord serum in Trujillo, Peru. Chemosphere 91 (10), 1426–1433.

Agency for Toxic Substances and Disease Registry (ATSDR), 2000. Toxicological Profile for Polychlorinated Biphenyls (PCBs). US Department of Health and Human Services, pp. 948.

Baccarelli, A., Pfeiffer, R., Consonni, D., Pesatori, A.C., Bonzini, M., Patterson, D.G., Bertazzi, P.A., Landi, M.T., 2005. Handling of dioxin measurement data in the presence of non-detectable values: overview of available methods and their application in the Seveso chloracne study. Chemosphere 60 (7), 898–906.

Beesoon, S., Martin, J.W., 2015. Isomer-specific binding affinity of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) to serum proteins. Environ. Sci. Technol. 49 (9), 5722–5731.

Berg, V., Nost, T.H., Pettersen, R.D., Hansen, S., Veyhe, A.S., Jorde, R., Odland, J.O., Sandanger, T.M., 2017. Persistent organic pollutants and the association with maternal and infant thyroid homeostasis: a multipollutant assessment. Environ. Health Perspect. 125 (1), 127–133.

Bjerregaard-Olesen, C., Long, M., Ghisari, M., Bech, B.H., Nohr, E.A., Uldbjerg, N., Henriksen, T.B., Olsen, J., Bonefeld-Jørgensen, E.C., 2017a. Temporal trends of lipophilic persistent organic pollutants in serum from Danish nulliparous pregnant women 2011–2013. Environ. Sci. Pollut. Res. 1–12.

Bjerregaard-Olesen, C., Bossi, R., Liew, Z., Long, M., Bech, B.H., Olsen, J., Henriksen, T.B., Berg, V., Nost, T.H., Zhang, J.J., Odland, J.O., Bonefeld-Jorgensen, E.C., 2017b. Maternal serum concentrations of perfluoroalkyl acids in five international birth cohorts. Int. J. Hyg. Environ. Health 220 (2 Pt A), 86–93.

Boas, M., Feldt-Rasmussen, U., Main, K.M., 2012. Thyroid effects of endocrine disrupting chemicals. Mol. Cell. Endocrinol. 355 (2), 240–248.

Bullo, M., Casas-Agustench, P., Amigo-Correig, P., Aranceta, J., Salas-Salvado, J., 2007. Inflammation, obesity and comorbidities: the role of diet. Public Health Nutr. 10 (10A), 1164–1172.

Butt, C.M., Miranda, M.L., Stapleton, H.M., 2016. Development of an analytical method to quantify PBDEs, OH-BDEs, HBCDs, 2, 4, 6-TBP, EH-TBB, and BEH-TEBP in human serum. Anal. Bioanal. Chem. 408 (10), 2449–2459.

Calado, R.T., Young, N.S., 2009. Telomere diseases. N. Engl. J. Med. 361 (24), 2353–2365.

Callahan, C.L., Pavuk, M., Birnbaum, L.S., Ren, X., Olson, J.R., Bonner, M.R., 2017. Serum polychlorinated biphenyls and leukocyte telomere length in a highly-exposed population: the Anniston Community Health Survey. Environ. Int. 108, 212–220.

Carrico, C., Gennings, C., Wheeler, D.C., Factor-Litvak, P., 2014. Characterization of weighted quantile sum regression for highly correlated data in a risk analysis setting. J. Agric. Biol. Environ. Stat. 20 (1), 100–120.

Centers for Disease Control and Prevention (CDC), 2009. Fourth National Report on Human Exposure to Environmental Chemicals.

Challis, J.R., Lockwood, C.J., Myatt, L., Norman, J.E., Strauss III, J.F., Petraglia, F., 2009. Inflammation and pregnancy. Reprod. Sci. 16 (2), 206–215.

Clougherty, J.E., Shmool, J.L., Kubzansky, L.D., 2014. The role of non-chemical stressors in mediating socioeconomic susceptibility to environmental chemicals. Curr. Environ. Health Rep. 1 (4), 302–313.

Coleman-Phox, K., Laraia, B.A., Adler, N., Vieten, C., Thomas, M., Epel, E., 2013. Recruitment and retention of pregnant women for a behavioral intervention: lessons from the maternal adiposity, metabolism, and stress (MAMAS) study. Prev. Chronic Dis. 10.

Cong, Y.S., Wright, W.E., Shay, J.W., 2002. Human telomerase and its regulation. Microbiol. Mol. Biol. Rev. 66 (3), 407–425.

Corsini, E., Sangiovanni, E., Avogadro, A., Galbiati, V., Viviani, B., Marinovich, M., Galli, C.L., Dell'Agli, M., Germolec, D.R., 2012. In vitro characterization of the immunotoxic potential of several perfluorinated compounds (PFCs). Toxicol. Appl. Pharmacol. 258 (2), 248–255.

Corwin, E.J., Pajer, K., 2008. The psychoneuroimmunology of postpartum depression. J. Women's Health 17 (9), 1529–1534.

Corwin, E.J., Johnston, N., Pugh, L., 2008. Symptoms of postpartum depression associated with elevated levels of interleukin-1 beta during the first month postpartum. Biol. Res. Nurs. 10 (2), 128–133.

Daniels, J.L., Pan, I.J., Jones, R., Anderson, S., Patterson, D.G., Needham, L.L., Sjodin, A., 2010. Individual characteristics associated with PBDE levels in US human milk samples. Environ. Health Perspect. 118 (1), 155–160.

DeWitt, J.C., Shnyra, A., Badr, M.Z., Loveless, S.E., Hoban, D., Frame, S.R., Cunard, R., Anderson, S.E., Meade, B.J., Peden-Adams, M.M., Luebke, R.W., Luster, M.I., 2009. Immunotoxicity of perfluorooctanoic acid and perfluorooctane sulfonate and the role of peroxisome proliferator-activated receptor alpha. Crit. Rev. Toxicol. 39 (1), 76–94.

DeWitt, J.C., Peden-Adams, M.M., Keller, J.M., Germolec, D.R., 2012. Immunotoxicity of perfluorinated compounds: recent developments. Toxicol. Pathol. 40 (2), 300–311.

Diamanti-Kandarakis, E., Bourguignon, J.P., Giudice, L.C., Hauser, R., Prins, G.S., Soto, A.M., Zoeller, R.T., Gore, A.C., 2009. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr. Rev. 30 (4), 293–342.

Fei, C.Y., McLaughlin, J.K., Tarone, R.E., Olsen, J., 2007. Perfluorinated chemicals and fetal growth: a study within the Danish National Birth Cohort. Environ. Health Perspect. 115 (11), 1677–1682.

Fisher, M., Arbuckle, T.E., Liang, C.L., LeBlanc, A., Gaudreau, E., Foster, W.G., Haines, D., Davis, K., Fraser, W.D., 2016. Concentrations of persistent organic pollutants in maternal and cord blood from the maternal-infant research on environmental chemicals (MIREC) cohort study. Environ. Health 15 (1), 59.

Geyer, H.J., Schramm, K.-W., Darnerud, P.O., Aune, M., Feicht, E.A., Fried, K.W., Henkelmann, B., Lenoir, D., Schmid, P., McDonald, T.A., 2004. Terminal elimination half-lives of the brominated flame retardants TBBPA, HBCD, and lower brominated PBDEs in humans. Organohalogen Compd. 66, 3867–3872.

Glynn, A., Berger, U., Bignert, A., Ullah, S., Aune, M., Lignell, S., Darnerud, P.O., 2012. Perfluorinated alkyl acids in blood serum from primiparous women in Sweden: serial sampling during pregnancy and nursing, and temporal trends 1996-2010. Environ. Sci. Technol. 46 (16), 9071–9079.

Gore, A.C., Chappell, V.A., Fenton, S.E., Flaws, J.A., Nadal, A., Prins, G.S., Toppari, J., Zoeller, R.T., 2015. Executive summary to EDC-2: the Endocrine Society's second scientific statement on endocrine-disrupting chemicals. Endocr. Rev. 36 (6), 593–602.

Graham, A.M., Rasmussen, J.M., Rudolph, M.D., Heim, C.M., Gilmore, J.H., Styner, M., Potkin, S.G., Entringer, S., Wadhwa, P.D., Fair, D.A., Buss, C., 2018. Maternal systemic interleukin-6 during pregnancy is associated with newborn amygdala phenotypes and subsequent behavior at 2 years of age. Biol. Psychiatry 83 (2), 109–119.

Guzzardi, M.A., Iozzo, P., Salonen, M.K., Kajantie, E., Airaksinen, R., Kiviranta, H., Rantakokko, P., Eriksson, J.G., 2016. Exposure to persistent organic pollutants predicts telomere length in older age: results from the Helsinki Birth Cohort Study. Aging Dis. 7 (5), 540–552.

Harrad, S., Diamond, M., 2006. New directions: exposure to polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs): current and future scenarios. Atmos. Environ. 40 (6), 1187–1188.

Haukas, M., Berger, U., Hop, H., Gulliksen, B., Gabrielsen, G.W., 2007. Bioaccumulation of per- and polyfluorinated alkyl substances (PFAS) in selected species from the Barents Sea food web. Environ. Pollut. (Barking, Essex: 1987) 148 (1), 360–371.

Haycock, P.C., Heydon, E.E., Kaptoge, S., Butterworth, A.S., Thompson, A., Willeit, P., 2014. Leucocyte telomere length and risk of cardiovascular disease: systematic review and meta-analysis. Br. Med. J. (Clin. Res. Ed.) g4227, 349.

Heindel, J.J., Newbold, R., Schug, T.T., 2015. Endocrine disruptors and obesity. Nat. Rev. Endocrinol. 11 (11), 653.

Helsel, D.R., 1990. Less than obvious - statistical treatment of data below the detection limit. Environ. Sci. Technol. 24 (12), 1766–1774.

Hennig, B., Meerarani, P., Slim, R., Toborek, M., Daugherty, A., Silverstone, A.E., Robertson, L.W., 2002. Proinflammatory properties of coplanar PCBs: in vitro and in vivo evidence. Toxicol. Appl. Pharmacol. 181 (3), 174–183.

Hou, L., Wang, S., Dou, C., Zhang, X., Yu, Y., Zheng, Y., Avula, U., Hoxha, M., Diaz, A., McCracken, J., Barretta, F., Marinelli, B., Bertazzi, P.A., Schwartz, J., Baccarelli, A.A., 2012. Air pollution exposure and telomere length in highly exposed subjects in Beijing, China: a repeated-measure study. Environ. Int. 48, 71–77.

Hu, W., Dong, T., Wang, L., Guan, Q., Song, L., Chen, D., Zhou, Z., Chen, M., Xia, Y., Wang, X., 2017. Obesity aggravates toxic effect of BPA on spermatogenesis. Environ. Int. 105, 56–65.

Iwama, H., Ohyashiki, K., Ohyashiki, J.H., Hayashi, S., Yahata, N., Ando, K., Toyama, K., Hoshika, A., Takasaki, M., Mori, M., 1998. Telomeric length and telomerase activity vary with age in peripheral blood cells obtained from normal individuals. Hum. Genet. 102 (4), 397–402.

Johnson, S.B., Riley, A.W., Granger, D.A., Riis, J., 2013. The science of early life toxic stress for pediatric practice and advocacy. Pediatrics 131 (2), 319–327.

Johnson, P.I., Sutton, P., Atchley, D.S., Koustas, E., Lam, J., Sen, S., Robinson, K.A., Axelrad, D.A., Woodruff, T.J., 2014. The Navigation Guide - evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. Environ. Health Perspect. 122 (10), 1028–1039.

Kojima, H., Takeuchi, S., Uramaru, N., Sugihara, K., Yoshida, T., Kitamura, S., 2009. Nuclear hormone receptor activity of polybrominated diphenyl ethers and their hydroxylated and methoxylated metabolites in transactivation assays using Chinese hamster ovary cells. Environ. Health Perspect. 117 (8), 1210–1218.

Kumar, J., Lind, P.M., Salihovic, S., van Bavel, B., Ingelsson, E., Lind, L., 2014. Persistent organic pollutants and inflammatory markers in a cross-sectional study of elderly Swedish people: the PIVUS cohort. Environ. Health Perspect. 122 (9), 977–983.

Lam, J., Lanphear, B.P., Bellinger, D., Axelrad, D.A., McPartland, J., Sutton, P., Davidson, L., Daniels, N., Sen, S., Woodruff, T.J., 2017. Developmental PBDE exposure and IQ/ADHD in childhood: a systematic review and meta-analysis. Environ. Health Perspect. 125 (8) (086001).

Leung, A.M., Korevaar, T.I., Peeters, R.P., Zoeller, R.T., Kohrle, J., Duntas, L.H., Brent, G.A., Demeneix, B.A., 2016. Exposure to thyroid-disrupting chemicals: a transatlantic call for action. Thyroid 26 (4), 479–480.

Leung, C.W., Laraia, B.A., Coleman-Phox, K., Bush, N.R., Lin, J., Blackburn, E.H., Adler, N.E., Epel, E.S., 2016. Sugary beverage and food consumption, and leukocyte telomere length maintenance in pregnant women. Eur. J. Clin. Nutr. 70 (9), 1086–1088.

Lin, J., Epel, E., Cheon, J., Kroenke, C., Sinclair, E., Bigos, M., Wolkowitz, O., Mellon, S., Blackburn, E., 2010. Analyses and comparisons of telomerase activity and telomere length in human T and B cells: insights for epidemiology of telomere maintenance. J. Immunol. Methods 352 (1–2), 71–80.

Liu, H., Tang, S., Zheng, X., Zhu, Y., Ma, Z., Liu, C., Hecker, M., Saunders, D.M., Giesy, J.P., Zhang, X., Yu, H., 2015. Bioaccumulation, biotransformation, and toxicity of BDE-47, 6-OH-BDE-47, and 6-MeO-BDE-47 in early life-stages of zebrafish (*Danio rerio*). Environ. Sci. Technol. 49 (3), 1823–1833.

Liu, D., Perkins, J.T., Petriello, M.C., Hennig, B., 2015. Exposure to coplanar PCBs induces endothelial cell inflammation through epigenetic regulation of NF-kappaB subunit p65. Toxicol. Appl. Pharmacol. 289 (3), 457–465.

Makki, K., Froguel, P., Wolowczuk, I., 2013. Adipose tissue in obesity-related

inflammation and insulin resistance: cells, cytokines, and chemokines. ISRN Inflamm. 2013, 139239.
Mitro, S.D., Johnson, T., Zota, A.R., 2015. Cumulative chemical exposures during pregnancy and early development. Curr. Environ. Health Rep. 2 (4), 367–378.
Mitro, S.D., Dodson, R.E., Singla, V., Adamkiewicz, G., Elmi, A.F., Tilly, M.K., Zota, A.R., 2016a. Consumer product chemicals in indoor dust: a quantitative meta-analysis of US studies. Environ. Sci. Technol. 50 (19), 10661–10672.
Mitro, S.D., Birnbaum, L.S., Needham, B.L., Zota, A.R., 2016b. Cross-sectional associations between exposure to persistent organic pollutants and leukocyte telomere length among U.S. adults in NHANES, 2001–2002. Environ. Health Perspect. 124 (5), 651–658.
Morello-Frosch, R., Cushing, L.J., Jesdale, B.M., Schwartz, J.M., Guo, W.H., Guo, T., Wang, M.M., Harwani, S., Petropoulou, S.S.E., Duong, W., Park, J.S., Petreas, M., Gajek, R., Alvaran, J., She, J.W., Dobraca, D., Das, R., Woodruff, T.J., 2016. Environmental chemicals in an urban population of pregnant women and their newborns from San Francisco. Environ. Sci. Technol. 50 (22), 12464–12472.
Moya, J., Phillips, L., Sanford, J., Wooton, M., Gregg, A., Schuda, L., 2014. A review of physiological and behavioral changes during pregnancy and lactation: potential exposure factors and data gaps. J. Expo. Sci. Environ. Epidemiol. 24 (5), 449–458.
Muezzinler, A., Zaineddin, A.K., Brenner, H., 2014. Body mass index and leukocyte telomere length in adults: a systematic review and meta-analysis. Obes. Rev. 15 (3), 192–201.
Mundstock, E., Sarria, E.E., Zatti, H., Mattos Louzada, F., Kich Grun, L., Herbert Jones, M., Guma, F.T., Mazzola In Memoriam, J., Epifanio, M., Stein, R.T., Barbe-Tuana, F.M., Mattiello, R., 2015. Effect of obesity on telomere length: systematic review and meta-analysis. Obesity (Silver Spring) 23 (11), 2165–2174.
O'Donovan, A., Pantell, M.S., Puterman, E., Dhabhar, F.S., Blackburn, E.H., Yaffe, K., Cawthon, R.M., Opresko, P.L., Hsueh, W.C., Satterfield, S., Newman, A.B., Ayonayon, H.N., Rubin, S.M., Harris, T.B., Epel, E.S., Health, A., Body Composition, S., 2011. Cumulative inflammatory load is associated with short leukocyte telomere length in the Health, Aging and Body Composition Study. PLoS One 6 (5), e19687.
Oikawa, S., Kawanishi, S., 1999. Site-specific DNA damage at GGG sequence by oxidative stress may accelerate telomere shortening. FEBS Lett. 453 (3), 365–368.
Olsen, G.W., Burris, J.M., Ehresman, D.J., Froehlich, J.W., Seacat, A.M., Butenhoff, J.L., Zobel, L.R., 2007. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. Environ. Health Perspect. 115 (9), 1298–1305.
Olsen, G.W., Mair, D.C., Lange, C.C., Harrington, L.M., Church, T.R., Goldberg, C.L., Herron, R.M., Hanna, H., Nobiletti, J.B., Rios, J.A., Reagen, W.K., Ley, C.A., 2017. Per- and polyfluoroalkyl substances (PFAS) in American Red Cross adult blood donors, 2000–2015. Environ. Res. 157, 87–95.
Pan, Y., Zhu, Y., Zheng, T., Cui, Q., Buka, S.L., Zhang, B., Guo, Y., Xia, W., Yeung, L.W., Li, Y., Zhou, A., Qiu, L., Liu, H., Jiang, M., Wu, C., Xu, S., Dai, J., 2017. Novel chlorinated polyfluorinated ether sulfonates and legacy per-/polyfluoroalkyl substances: placental transfer and relationship with serum albumin and glomerular filtration rate. Environ. Sci. Technol. 51 (1), 634–644.
Park, H.R., Loch-Caruso, R., 2014. Protective effect of nuclear factor E2-related factor 2 on inflammatory cytokine response to brominated diphenyl ether-47 in the HTR-8/SVneo human first trimester extravillous trophoblast cell line. Toxicol. Appl. Pharmacol. 281 (1), 67–77.
Park, H.R., Kamau, P.W., Loch-Caruso, R., 2014. Involvement of reactive oxygen species in brominated diphenyl ether-47-induced inflammatory cytokine release from human extravillous trophoblasts in vitro. Toxicol. Appl. Pharmacol. 274 (2), 283–292.
Peltier, M.R., Klimova, N.G., Arita, Y., Gurzenda, E.M., Murthy, A., Chawala, K., Lerner, V., Richardson, J., Hanna, N., 2012. Polybrominated diphenyl ethers enhance the production of proinflammatory cytokines by the placenta. Placenta 33 (9), 745–749.
Phillips, D.L., Pirkle, J.L., Bernert, J.T., Henderson, L.O., Needham, L.L., 1989. Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. Arch. Environ. Contam. Toxicol. 18 (4), 495–500.
Ritter, R., Scheringer, M., MacLeod, M., Moeckel, C., Jones, K.C., Hungerbuhler, K., 2011. Intrinsic human elimination half-lives of polychlorinated biphenyls derived from the temporal evolution of cross-sectional biomonitoring data from the United Kingdom. Environ. Health Perspect. 119 (2), 225–231.
Romero, R., Espinoza, J., Gonçalves, L.F., Kusanovic, J.P., Friel, L., Hassan, S., 2007. The role of inflammation and infection in preterm birth. Semin. Reprod. Med. 25 (01), 021–039.
Rubin, D.B., 1987. Multiple Imputation for Nonresponse in Surveys. Wiley, New York.
Shalev, I., Entringer, S., Wadhwa, P.D., Wolkowitz, O.M., Puterman, E., Lin, J., Epel, E.S., 2013. Stress and telomere biology: a lifespan perspective. Psychoneuroendocrinology 38 (9), 1835–1842.
Shin, J.Y., Choi, Y.Y., Jeon, H.S., Hwang, J.H., Kim, S.A., Kang, J.H., Chang, Y.S., Jacobs Jr., D.R., Park, J.Y., Lee, D.H., 2010. Low-dose persistent organic pollutants increased telomere length in peripheral leukocytes of healthy Koreans. Mutagenesis 25 (5), 511–516.
Smith, S.E., Li, J., Garbett, K., Mirnics, K., Patterson, P.H., 2007. Maternal immune activation alters fetal brain development through interleukin-6. J. Neurosci. 27 (40), 10695–10702.
Tee, P.G., Sweeney, A.M., Symanski, E., Gardiner, J.C., Gasior, D.M., Schantz, S.L., 2003. A longitudinal examination of factors related to changes in serum polychlorinated biphenyl levels. Environ. Health Perspect. 111 (5), 702–707.
Tukey, J.W., 1977. Exploratory Data Analysis. Addison-Wesley, Reading, MA.
Turyk, M., Fantuzzi, G., Persky, V., Freels, S., Lambertino, A., Pini, M., Rhodes, D.H., Anderson, H.A., 2015. Persistent organic pollutants and biomarkers of diabetes risk in a cohort of Great Lakes sport caught fish consumers. Environ. Res. 140, 335–344.
United States Environmental Protection Agency (US EPA), 2014. Technical Fact Sheet – Polybrominated Diphenyl Ethers (PBDEs) and Polybrominated Biphenyls (PBBs).
United States Environmental Protection Agency (US EPA), 2017. Basic Information About Per- and Polyfluoroalkyl Substances (PFASs).
Usenko, C.Y., Robinson, E.M., Usenko, S., Brooks, B.W., Bruce, E.D., 2011. PBDE developmental effects on embryonic zebrafish. Environ. Toxicol. Chem. 30 (8), 1865–1872.
Usenko, C.Y., Hopkins, D.C., Trumble, S.J., Bruce, E.D., 2012. Hydroxylated PBDEs induce developmental arrest in zebrafish. Toxicol. Appl. Pharmacol. 262 (1), 43–51.
Vohr, B.R., Poggi Davis, E., Wanke, C.A., Krebs, N.F., 2017. Neurodevelopment: the impact of nutrition and inflammation during preconception and pregnancy in low-resource settings. Pediatrics 139 (Suppl. 1), S38–S49.
Vuong, A.M., Webster, G.M., Romano, M.E., Braun, J.M., Zoeller, R.T., Hoofnagle, A.N., Sjodin, A., Yolton, K., Lanphear, B.P., Chen, A., 2015. Maternal polybrominated diphenyl ether (PBDE) exposure and thyroid hormones in maternal and cord sera: the HOME study, Cincinnati, USA. Environ. Health Perspect. 123 (10), 1079–1085.
Wang, M., Park, J.S., Petreas, M., 2011. Temporal changes in the levels of perfluorinated compounds in California women's serum over the past 50 years. Environ. Sci. Technol. 45 (17), 7510–7516.
Wiegers, G.J., Reul, J.M., 1998. Induction of cytokine receptors by glucocorticoids: functional and pathological significance. Trends Pharmacol. Sci. 19 (8), 317–321.
Wild, C.P., 2012. The exposome: from concept to utility. Int. J. Epidemiol. 41 (1), 24–32.
Willeit, P., Raschenberger, J., Heydon, E.E., Tsimikas, S., Haun, M., Mayr, A., Weger, S., Witztum, J.L., Butterworth, A.S., Willeit, J., Kronenberg, F., Kiechl, S., 2014. Leucocyte telomere length and risk of type 2 diabetes mellitus: new prospective cohort study and literature-based meta-analysis. PLoS One 9 (11), e112483.
Woodruff, T.J., Zota, A.R., Schwartz, J.M., 2011. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. Environ. Health Perspect. 119 (6), 878–885.
Yang, Q., Wang, W., Liu, C., Wang, Y., Sun, K., 2016. Effect of PFOS on glucocorticoid-induced changes in human decidual stromal cells in the first trimester of pregnancy. Reprod. Toxicol. (Elmsford, N.Y.) 63, 142–150.
Yuan, Y., Meeker, J.D., Ferguson, K.K., 2017. Serum polybrominated diphenyl ether (PBDE) concentrations in relation to biomarkers of oxidative stress and inflammation: the National Health and Nutrition Examination Survey 2003–2004. Sci. Total Environ. 575, 400–405.
Zhang, X., Lin, S., Funk, W.E., Hou, L., 2013. Environmental and occupational exposure to chemicals and telomere length in human studies. Occup. Environ. Med. 70 (10), 743–749.
Zhang, J.Y., Zhang, J., Liu, R., Gan, J., Liu, J., Liu, W.P., 2016. Endocrine-disrupting effects of pesticides through interference with human glucocorticoid receptor. Environ. Sci. Technol. 50 (1), 435–443.
Zota, A.R., Rudel, R.A., Morello-Frosch, R.A., Brody, J.G., 2008. Elevated house dust and serum concentrations of PBDEs in California: unintended consequences of furniture flammability standards? Environ. Sci. Technol. 42 (21), 8158–8164.
Zota, A.R., Park, J.S., Wang, Y., Metreas, M., Zoeller, R.T., Woodruff, T.J., 2011. Polybrominated diphenyl ethers, hydroxylated polybrominated diphenyl ethers, and measures of thyroid function in second trimester pregnant women in California. Environ. Sci. Technol. 45, 7896–7905.
Zota, A.R., Linderholm, L., Park, J.S., Petreas, M., Guo, T., Privalsky, M.L., Zoeller, R.T., Woodruff, T.J., 2013. Temporal comparison of PBDEs, OH-PBDEs, PCBs, and OH-PCBs in the serum of second trimester pregnant women recruited from San Francisco General Hospital, California. Environ. Sci. Technol. 47 (20), 11776–11784.
Zota, A.R., Needham, B.L., Blackburn, E.H., Lin, J., Park, S.K., Rehkopf, D.H., Epel, E.S., 2015. Associations of cadmium and lead exposure with leukocyte telomere length: findings from National Health and Nutrition Examination Survey, 1999–2002. Am. J. Epidemiol. 181 (2), 127–136.
Zota, A.R., Phillips, C.A., Mitro, S.D., 2016. Recent fast food consumption and bisphenol A and phthalates exposures among the U.S. population in NHANES, 2003–2010. Environ. Health Perspect. 124 (10), 1521–1528.