Title

Persistent organic pollutants and maternal glycemic outcomes in a diverse pregnancy cohort of overweight women

Authors

Mehta, Suril S
James-Todd, Tamarra
Applebaum, Katie M
et al.

Publication Date

2021-02-01

DOI

10.1016/j.envres.2020.110551

Peer reviewed

HHS Public Access

Author manuscript

Environ Res. Author manuscript; available in PMC 2022 February 01.

Published in final edited form as:

Environ Res. 2021 February ; 193: 110551. doi:10.1016/j.envres.2020.110551.

Persistent organic pollutants and maternal glycemic outcomes in a diverse pregnancy cohort of overweight women

Suril S. Mehta[1], **Tamarra James-Todd**[2,3], **Katie M. Applebaum**[1], **Andrea Bellavia**[2], **Kimberly Coleman-Phox**[4], **Nancy Adler**[5], **Barbara Laraia**[6], **Elissa Epel**[5], **Emily Parry**[7], **Miaomiao Wang**[7], **June-Soo Park**[7], **Ami R. Zota**[1]

[1]Department of Environmental and Occupational Health, Milken Institute School of Public Health, The George Washington University, Washington, DC, USA

[2]Department of Environmental Health, T.H. Chan School of Public Health, Harvard University, Boston, MA, USA

[3]Department of Epidemiology, T.H. Chan School of Public Health, Harvard University, Boston, MA, USA

[4]Center for Health and Community, School of Medicine, University of California, San Francisco, San Francisco, CA, USA

[5]Department of Psychiatry, School of Medicine, University of California, San Francisco, San Francisco, CA, USA

[6]Division of Community Health and Human Development, School of Public Health, University of California, Berkeley, Berkeley, CA, USA

[7]Environmental Chemistry Laboratory, California Department of Toxic Substances Control, Berkeley, CA, USA

Abstract

Background: Animal and human studies suggest certain persistent organic pollutants (POPs) may impact glucose metabolism; however, few epidemiologic studies have examined

Corresponding author: Suril S. Mehta, surilsm@gwu.edu. 202-441-0766. Department of Environmental and Occupational Health, Milken Institute School of Public Health, The George Washington University.

CRediT author statement

S.S.M.: Conceptualization, Methodology, Formal Analysis, Writing - Original Draft, Writing - Review & Editing. **T.J-T.:** Conceptualization, Methodology, Writing - Review & Editing. **K.M.A.:** Conceptualization, Methodology, Writing - Review & Editing. **A.B.:** Methodology, Formal Analysis. **K.C-P.:** Investigation, Data Curation, Writing - Review & Editing. **N.A.:** Investigation, Resources, Data Curation, Writing - Review & Editing. **B.L.:** Investigation, Resources, Data Curation, Writing - Review & Editing. **E.E.:** Investigation, Resources, Data Curation . **E.P.:** Investigation, Resources, Data Curation. **M.W.:** Investigation, Resources, Data Curation. **J-S.P.:** Investigation, Resources, Data Curation, Writing - Review & Editing. **A.R.Z.:** Conceptualization, Methodology, Formal Analysis, Writing - Review & Editing, Supervision.

Declaration of interests

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

Conflict of interest statement: The authors declare that they have no conflict of interest.

environmental determinants of glycemic outcomes during pregnancy. Our objective is to evaluate associations between exposures to individual and mixture of POPs and measures of prenatal fasting glucose, insulin, and insulin resistance during pregnancy in overweight women.

Methods: A cohort of overweight and obese pregnant women (N = 95) was recruited from California. Blood samples were collected during late first or second trimester (median = 16 weeks' gestation; range = 10–24 weeks). Exposures included serum concentrations of polybrominated diphenyl ethers (PBDEs) and hydroxylated metabolites (OH-PBDEs), polychlorinated biphenyls (PCBs), and poly- and perfluoroalkyl substances (PFASs). Outcomes included serum concentrations of fasting plasma glucose, fasting plasma insulin, and calculated homeostatic model assessment of insulin resistance (HOMA-IR). Generalized linear models were used to evaluate cross-sectional associations between individual and aggregate POPs and mean percent difference in fasting glucose, fasting insulin, and HOMA-IR. Bayesian kernel machine regression (BKMR) was used to assess the relative importance of each exposure to the association with our outcomes, using conditional and group posterior inclusion probabilities (PIPs).

Results: Study participants were racially/ethnically diverse and nearly half were below the federal poverty level. Across PBDEs and OH-PBDEs, the direction of associations with fasting glucose, fasting insulin and HOMA-IR were varied. A doubling of PCB-138, PCB-153, PCB-180, and ΣPCBs concentrations was associated with a 2.10% mmol/L (95%CI: 0.49%, 3.74%), 2.10% mmol/L (95%CI: −0.14%, 4.39%), 2.10% mmol/L (95%CI: 0.12%, 4.12%), and 2.81% mmol/L (95%CI: 0.38%, 5.31%) increase in fasting glucose, respectively. Exposure to individual PCBs was positively associated with both fasting insulin and HOMA-IR. All PFAS were inversely associated with fasting glucose, fasting insulin, and HOMA-IR. In BKMR models of fasting glucose, all four chemical classes were important contributors to the overall mixture, with PFASs identified as the most important contributor.

Discussion: Prenatal PCB exposure was positively associated while certain PBDE and PFAS analytes were inversely associated with fasting glucose concentrations in overweight women. Further examination of the relationship between POPs exposure and glycemic functioning in a larger study population of women during pregnancy is warranted.

1. Introduction

Impaired glucose homeostasis during pregnancy, including hyperglycemia, pronounced insulin resistance, and hyperinsulinemia, can lead to adverse maternal cardiometabolic outcomes, pregnancy-related hypertension and gestational diabetes mellitus (GDM). A disease characterized by glucose intolerance first recognized at onset during pregnancy, GDM has increased over the past few decades in the United States (Lavery et al. 2017). Women with GDM are at an increased risk for pregnancy-related complications and type 2 diabetes mellitus in the years following pregnancy. GDM can also impact infant health, including premature birth, macrosomia, stillbirth, hypoglycemia, and jaundice (Xiong et al. 2001). Established risk factors for GDM include, older maternal age, pre-pregnancy overweight or obesity, family history of diabetes, and non-white race or ethnicity (Hunt and Schuller 2007).

Environmental chemical exposures, including persistent organic pollutants (POPs), are also implicated as playing a role in glucose dysregulation and GDM during pregnancy (Rahman et al. 2019). In experimental studies, POPs have been shown to disrupt the body's regulation of glucose homeostasis by activating certain nuclear (e.g., peroxisome proliferator-activated receptors) and hormone (e.g., estrogen) receptors that play critical roles in metabolic regulation (Diamanti-Kandarakis et al. 2009). Bioaccumulative and hazardous POPs such as per- and polyfluoroalkyl substances (PFASs), polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs) are highly prevalent in pregnant women, despite efforts to reduce their use in industrial processes, manufacturing, and consumer products over the past few decades (Woodruff et al. 2011, Parry et al. 2018). Our prior work suggests exposure to contemporary and phased out POPs in U.S. pregnant women is ongoing (Mehta et al 2019). These chemical groups are suspected to disrupt the metabolic system through receptor binding, hormone receptor activation, and alterations in hormonal balance (Casals-Casals and Desvergne 2010).

In human observational studies, the association of POPs during pregnancy with maternal glycemic functioning is still unclear. Results are inconsistent for PFASs and GDM (Zhang et al. 2015, Shapiro et al. 2016, Smarr et al. 2016, Matilla-Santander et al. 2017, Valvi et al. 2017, Liu et al. 2019, Rahman et al. 2019, Preston et al. 2020), PBDEs (Eslami et al. 2016, Smarr et al. 2016, Liu et al. 2018, Rahman et al. 2019), and PCBs (Jaacks et al. 2016, Shapiro et al. 2016, Valvi et al. 2017, Vafeiadi et al. 2017, Zhang et al. 2018, Rahman et al. 2019); often one, but not all of the chemicals within a chemical class show an association with increased risk of GDM. Additionally, few studies have examined the relationship with more than one class of POPs or a mixture of POPs (Smarr et al. 2016, Shapiro et al. 2016, Rahman et al. 2019). Moreover, few studies have examined the glycemic indicators used to screen and diagnose GDM, such as blood glucose and/or insulin, as outcomes (Liu et al. 2018, Zhang et al. 2018, Liu et al. 2019). Indeed, subtler changes in glucose metabolism based on elevations in blood glucose or insulin levels that could result from higher exposure to POPs could be indicative of future adverse cardiometabolic outcomes in both women and their children. In fact, studies have shown that elevated glucose levels that do not meet the clinical threshold for GDM are associated with an increased risk of obesity and insulin resistance in the offspring (Lowe et al. 2019; Scholtens et al. 2019).

While prior studies have evaluated associations between exposure to POPs and GDM diagnosis, the association of these POPs and more sensitive markers of glucose dysregulation have not been evaluated as readily, particularly among high-risk pregnancies, such as women who are overweight or obese prior to pregnancy. More than half of U.S. women are overweight or obese prior to pregnancy (Deputy et al. 2018), with a two to eight times increased risk of GDM compared to women with a normal pre-pregnancy weight (Chu et al. 2007). Further, obese pregnant women without diabetes have higher insulin than pregnant women of normal weight (Harmon et al. 2011, Barrett et al. 2014).

Accordingly, to address these multiple data gaps, the objective of our study was to investigate the relationship between individual and aggregate POPs and indicators of glycemic functioning, including glucose, insulin, and insulin resistance, in a group of overweight and obese pregnant women. Further, we employed a supervised mixtures

method, Bayesian kernel machine regression (BKMR), to examine the impact of chemical mixtures on our outcomes.

2. Methods

2.1. Study population

Our study population consists of a subset of pregnant women enrolled in the Maternal Adiposity, Metabolism, and Stress (MAMAS) study, a gestational weight gain intervention study for overweight and obese pregnant women living in or around San Francisco, California. The intervention's goal was to control weight gain during pregnancy through reduced stress techniques (NC01307683 on www.clincicaltrials.gov). Details on the recruitment and intervention can be found elsewhere (Coleman-Phox et al. 2013, Vieten et al. 2018).

Eligible participants in the MAMAS study were pregnant women between 8–23 weeks' gestation, 18–45 years old, with an annual household income <500% of the 2011 Federal poverty level, and a self-reported pre-pregnancy body mass index (BMI) between 25–40 kg/m^2. BMI was confirmed via medical records. Seven eligible participants were subsequently identified through medical record confirmation as having a pre-pregnancy BMI between 23.0 and 25.0 kg/m^2, but were included in the intervention. Women were excluded from study participation for a variety of health and behavioral factors, including pre-existing diabetes or Metformin use; more detailed exclusion criteria can be found elsewhere (Vieten et al. 2018).

This study was approved by the University of California, San Francisco Committee on Human Research and the California Pacific Medical Center Institutional Review Board (IRB), University of California, Berkeley, and Contra Costa Regional Medical Center and Health Centers IRB. Informed consent was obtained from all participants.

Of the 215 participants in the MAMAS study, we only focus on women who participated in the intervention arm for which additional biological samples were available for analysis of environmental chemicals (N=106). We excluded women who were not pregnant (N=1), did not have chemical biomarker data (N=2), and did not have information on outcomes (N=1) or covariates of interest (N=7), leaving 95 participants.

2.2. Maternal POPs concentrations

Trained UCSF staff collected a 10 mL fasting maternal blood sample at the baseline visit (10–24 weeks' gestation) in an additive-free red top tube (BD Vacutainer). Blood was allowed to clot for 1 h, then placed on ice for a subsequent 1 h. Samples were centrifuged at 1300g for 10 min at 4°C, 1 mL serum was aliquoted into five vials, and samples were stored at −80°C for up to three months.

Analysis of collected serum for individual PBDE congeners, hydroxylated PBDE metabolites (OH-PBDEs), PCB congeners, and PFAS analytes were completed at the analytical laboratory at the Department of Toxic Substances Control (Berkeley, CA, USA). Additional details on analytical laboratory methods, including sample extraction,

instrumentation and procedures, validation, and quality control on the study samples can be found elsewhere (Zota et al. 2018). Briefly, serum samples were analyzed for 19 PBDEs, 8 OH-PBDEs, and 15 PCBs. Sample extraction and analytical methods for PBDEs, OH-PBDEs, and PCBs were performed based on commonly used techniques (Hovander et al. 2000). An online solid phase extraction liquid chromatography tandem mass spectrometry (SPE-LC-MS/MS) method was employed to quantify concentrations of PFAS analytes in maternal serum. OH-PBDE, PBDE and PCB congener concentrations were measured using gas chromatography/ high-resolution mass spectrometry (GC-HRMS). Serum lipid analysis was conducted at Boston Children's Hospital. Phillips formula (Phillips et al. 1989) was used to calculate total serum lipids based on measured total cholesterol and triglycerides. To address inter-individual variability of wet-weight chemical concentrations, PBDE and PCB concentrations were normalized by total serum lipids (ng/g lipid). OH-PBDE and PFAS concentrations were reported as wet-weight concentrations (ng/mL).

The following individual POPs had a detection frequency (DF) ≥ 50% of the methodological detection limit (MDL) and were included in our analyses: BDE-47, −99, −100, −153, 5-OHBDE-47, 6-OHBDE-47, PCB-138, −153, −180, perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDeA), and perfluorohexane sulfonate (PFHxS). For these 14 chemicals, we used a distribution-based multiple imputation "fill in" method described elsewhere (Zota et al. 2011, Baccarelli et al. 2005; Helsel et al. 1990). For concentrations below the MDL, we fit a log-normal probability distribution whose parameters were calculated using maximum likelihood estimation, then subsequently imputed nondetect values. We analyzed congeners or analytes by summing within chemical group, leaving ΣPBDEs, ΣOH-PBDEs, ΣPCBs, and ΣPFASs. Correlations within and across chemical groups were assessed using Spearman correlation.

2.3. Outcome assessment

As part of a comprehensive metabolic panel collected at baseline, a fasting blood draw of 5 mL was centrifuged in a serum-separating tube for 10 minutes, placed on ice, then five 1 mL aliquots were sent to Quest Diagnostics for spectrophotometry. Serum fasting plasma glucose (mmol/L) and serum fasting plasma insulin (pmol/L) were collected. Insulin resistance was determined using the homeostatic model assessment for insulin resistance (HOMA-IR) using the formula by Levy et al. (1998) based on fasting glucose and insulin.

We were unable to use information from GDM screening and/or diagnostic testing abstracted via medical records due to substantial missing data. Specifically, blood glucose measures from the two-step method typically used to diagnose GDM were incomplete (initial clinical screening using a 1-hour nonfasting oral glucose loading test using 50g bolus [N=78] and, if warranted, a subsequent diagnostic 3-hour fasting oral glucose tolerance test using 100g bolus [N=32]). Furthermore, <10% of the study population (N=7) reported a diagnosis of GDM based on medical records; therefore, GDM diagnosis was not included as an outcome of interest.

2.4. Covariates

Sociodemographic and behavioral information were collected via an in-person or phone-based questionnaire administered at baseline. The questionnaire can be found elsewhere (Vieten et al. 2018). Gestational age at enrollment and estimated delivery date were affirmed using abstracted medical records, if available. Food security was measured with the ten-item adult Food Security Scale in the baseline questionnaire for all participants (Bickel et al. 2001), then dichotomized into marginal-to-high food security (i.e., food secure households) and low-to-very low food security (i.e., food insecure households). All participants had information on gestational age and BMI at baseline measurement, though pre-pregnancy BMI was missing for four participants. Previously, we reported the strong correlation between pre-pregnancy and baseline BMI (Mehta et al. 2019). Among those who had complete BMI measures (pre-pregnancy and baseline), we generated a linear regression model with pre-pregnancy BMI as the dependent variable and age and BMI at baseline as independent variables. We verified that the model closely predicted the pre-pregnancy BMI in those with non-missing values and then used the coefficients from the model to provide an estimated value of the pre-pregnancy BMI for the four subjects missing pre-pregnancy BMI (e.g., applied individual age and baseline BMI to the estimated coefficients).

2.5. Statistical analysis

We calculated geometric means and geometric standard errors for all chemicals and outcomes of interest (fasting glucose, fasting insulin, HOMA-IR). All biochemical indicators of glycemic homeostasis are presented continuously. Both exposure and outcome biomarkers were natural log-transformed to normalize the distribution. The association between chemical concentrations and our outcomes of interest were examined using multivariable linear regression. To highlight the incremental change in biochemical concentrations, results were reported as the percent difference in fasting glucose, fasting insulin or HOMA-IR associated with a doubling of serum chemical concentrations, calculated as $(\exp[\beta \times \ln(2)] - 1) \times 100\%$, and 95% confidence intervals (95%CI) calculated as $(\exp[\ln(2) \times (\beta \pm 1.96 \times SE)] - 1) \times 100\%$.

Informed by a prior analysis on factors of importance to this population (Mehta et al. 2019), we identified sociodemographic and biological variables to control for in multivariable models, including race/ethnicity (Non-Hispanic White or other, Non-Hispanic Black, Latina), maternal age at enrollment (in years), gestational age at baseline (in weeks), household income (≤ or > 100% of the 2011 federal poverty line, accounting for household size), pre-pregnancy BMI (kg/m^2; continuous), and parity (count).

Additional sensitivity analyses were conducted to include food security (marginal/high or low/very low food security households) and educational attainment (≤ high school graduate or > high school graduate), as these sociodemographic variables were previously shown to be associated with chemical exposures in this population (Mehta et al. 2019).

2.5.1. Multipollutant models—Our previous analysis identified exposure to multiple POPs within our study population, with high within-class and low across-class correlation (Mehta et al. 2019). To better understand the association of POPs and glycemic outcomes in

the context of a complex mixture, we ran multipollutant models. To account for the high within-chemical class correlation in our study population (Mehta et al. 2019), our first multipollutant model expanded our multivariable linear regression models to include additional terms to control for ΣPBDEs, ΣOH-PBDEs, ΣPCBs, and ΣPFASs.

Our second multipollutant model employed BKMR, a supervised mixtures method that estimates exposure-response relationships based on the relationship of components in a mixture to a particular outcome, while accounting for multicollinearity. BKMR incorporates a variable selection approach within the estimation of individual dose-response associations, accounting for potential non-linear relationships (Bobb et al. 2015, Bobb et al. 2019). The mixture-outcome association is evaluated by using a Gaussian kernel function within a Bayesian framework. The variable selection procedure is assessed with posterior inclusion probabilities (PIPs), which depict the relative importance of each exposure in the association. We used a hierarchical version of BKMR, grouping our 14 highly detected POPs into three groupings: PBDEs/OH-PBDEs, PCBs, and PFASs. This estimates the relative importance of each chemical group (group PIPs), as well as the conditional contribution of each chemical within groups (conditional PIPs). We considered chemical groups with a group PIP >0.50 important to the overall exposure-response of the mixture. Conditional PIPs examine the ranking of each chemical being selected within the chemical group. Next, we estimated individual dose-responses associations for each chemical, as well as potential interactions; however, no significant results were observed in this analysis (data not shown). We evaluate hierarchical BKMR using 50,000 iterations of a Markov chain Monte Carlo algorithm, controlling for race/ethnicity, maternal age, gestational age at baseline, household income, pre-pregnancy BMI, and parity, and estimating and presenting group and conditional PIPs. All log-transformed chemical concentrations and glycemic outcomes were standardized prior to BKMR.

All statistical analyses were completed in SAS version 9.4 (Cary, NC) and R version 3.6.2 (cran.r-project.org), with BKMR completed using the ‘bkmr’ package.

3. Results

Detection frequencies, geometric means, and correlations of maternal serum POPs concentrations are presented in Table 1 and Supplemental Table S1. More than 90% of maternal serum samples had detectable concentrations of BDE-47, BDE-153, PFNA, PFOS, PFOA, and PFHxS. The study population was racially and ethnically diverse, 45.3% had a household income at or below 100% of the Federal poverty level, and 49.5% had an obese BMI (Table 2). Participants were mostly enrolled in their 2nd trimester and half were nulliparous. The geometric mean of concentrations of fasting glucose was 4.42 ± 0.04 mmol/L, fasting insulin was 81.19 ± 4.73 pmol/L, and HOMA-IR was 1.65 ± 0.09 units. When examining our continuous outcomes by variables of interest, higher fasting glucose was associated with increasing maternal age. Women with a BMI >30 kg/m^2 had higher concentrations of fasting glucose, insulin, and HOMA-IR.

3.1. Individual and class-specific models

In multivariable models of individual and summed chemical concentrations and fasting glucose (Figure 1; Supplemental Table S2), we observed positive associations with PCBs, and inverse associations with PFASs and most PBDEs and OH-PBDEs. A doubling of BDE-153 and 5-OHBDE-47 were associated with a decrease in fasting glucose. For PFASs, PFNA, PFOS, PFOA, and ΣPFASs were all associated with a decrease in fasting glucose. Conversely, all PCBs were positively associated with fasting glucose, including PCB-138 (2.10% mmol/L [95%CI: 0.49%, 3.74%]), PCB-153 (2.10% mmol/L [95%CI: −0.14%, 4.39%]), PCB-180 (2.10% mmol/L [95%CI: 0.12%, 4.12%]), and ΣPCBs (2.81% mmol/L [95%CI: 0.38%, 5.31%]). For fasting insulin and insulin resistance (HOMA-IR) (Supplemental Figures S1 and S2; Supplemental Table 2), the direction of association was consistent with results from the fasting glucose models; positive for all PCBs, inversely associated with PFASs and most PBDEs/OH-PBDEs but ΣPBDEs and 6-OHBDE-47, which saw nonsignificant positive associations. The strongest associations for fasting insulin and insulin sensitivity (HOMA-IR) were seen for PCB-138; doubling of PCB-138 show a borderline significant positive percent difference in fasting insulin (9.43% mmol/L [95%CI: −0.96%, 20.91%], p=0.07) and HOMA-IR (10.19% mmol/L [95%CI: 0.10%, 21.30%], p=0.05).

Results were generally similar when food security and educational attainment were added as additional covariates to our models (Supplemental Table S3).

3.2. Multipollutant models

In our multipollutant linear regression models (Supplemental Table S4), effect estimates were similar to single-pollutant models. Applying BKMR model approach to estimate fasting glucose, we found that all three chemical groupings were important to the overall mixture (Table 3), with the PFAS group being the most important contributor (group PIP = 0.79). Of the PBDEs/OH-PBDEs, both BDE-153 and 5-OHBDE-47 had the highest conditional PIPs (39% and 30%, respectively). All three PCBs had roughly 1/3rd probability of inclusion in the model. Among the PFASs, PFNA had the highest conditional PIP (58%), followed by PFOS (20%). Our BKMR models of fasting insulin and insulin resistance (HOMA-IR) (Supplemental Tables S5 and S6) similarly found the PFAS group to be the most important contributor to the overall mixture (group PIP=0.78 and 0.79, respectively), with PFNA having the highest conditional PIP among the PFAS analytes (54% and 49%, respectively).

4. Discussion

In our small cross-sectional study of exposure to POPs and markers of maternal glucose metabolism in a group of overweight and obese pregnant women, we found variability in both direction and magnitude of association between individual chemicals and fasting glucose, insulin, and insulin resistance. Individual and aggregate PCBs were positively associated with fasting glucose and insulin, as well as insulin resistance in maternal serum measured in early pregnancy. The positive associations between PCBs and fasting glucose were largely unchanged after adjustment for other chemical classes. On the other hand,

maternal PFAS concentrations were inversely associated with all three fasting glycemic measures. In particular, a doubling of PFNA, PFOS, PFOA and ΣPFASs were inversely associated with maternal fasting glucose in single and multipollutant models. PBDEs and OH-PBDEs, specifically BDE-153 and 5-OHBDE-47, were also inversely associated with fasting glucose in single and multipollutant models.

Heterogeneity in the magnitude and direction of our associations across individual chemicals from four chemical exposure groups largely mirrors the lack of consistency in published literature. Studies examining the association between PFASs, PBDEs, OH-PBDEs, and/or PCBs and biochemical indicators of abnormal glucose metabolism during pregnancy have been conducted (Liu et al. 2018, Zhang et al. 2018, Wang et al. 2018, Liu et al. 2019, Preston et al. 2020), though most report fasting glucose values of the oral glucose tolerance test for GDM diagnosis. We found positive associations between prenatal PCB concentrations and glycemic indicators across all analyses. Despite our limited sample size, our results may indicate PCB exposure is involved in glucose dysregulation during pregnancy. In contrast, a Chinese nested case-control study (Zhang et al. 2018) did not find any associations with PCB-138, −153, and −180 and fasting glucose during pregnancy. Animal studies have linked PCB exposure to insulin resistance and impaired glucose tolerance (Wahlang et al. 2013; Gray et al. 2013). The biological mechanisms by which PCBs may impact glucose homeostasis have yet to be determined, though aryl hydrocarbon receptor (AhR) activation is suspected to play a role (Casals-Casas and Desvergne 2010). Mechanistic studies suggest PCBs act via AhR activation resulting in increased insulin resistance and glucose homeostasis (Remillard and Bunce 2002; Baker et al. 2015).

Similarly, our BDE-153 findings are discordant with a nested case-control study that reported a 3.10% increase in fasting glucose (95%CI: 0.95%, 5.31%) associated with a doubling of BDE-153 (Liu et al. 2018). Preconception BDE-153 and BDE-47 concentrations in a US cohort were positively and inversely associated with GDM, respectively (Smarr et al. 2016). One explanation for the differences seen may be due to the higher proportion of overweight and obese women in our study; our study population could be differentially impacted by these metabolic disruptors as it relates to our glycemic outcomes. Given the inconsistent results across studies, further investigation of PBDEs and both fasting measures and gestational diabetes is needed.

In our study, all PFASs were inversely associated with all glycemic outcomes. There are few studies to compare our results to because most other studies did not include fasting measures of glucose, insulin, and insulin resistance during pregnancy. A U.S.-based pregnancy cohort found positive associations with PFOS and nonfasting plasma glucose concentrations from the glucose loading test at late second trimester (Preston et al. 2020). Further, Preston et al. found suggestive evidence of differences by race/ethnicity. Among populations outside of the U.S. using fasting measures, a prospective study (Wang et al. 2018) found significant positive associations between PFOA and both fasting insulin and HOMA-IR among pregnant women in China. Another study among Chinese pregnant women examining fasting glucose found inverse associations with PFOS, long-chained perfluoroalkyl sulfonates, and perfluoroalkyl carboxylates, and positive association with PFOA (Liu et al. 2019). Both PFOS and PFOA have been found to activate the peroxisome proliferator-

activated receptor alpha (PPARα), a nuclear receptor in animals involved in the regulation of lipid and glucose homeostasis (Takacs and Abbott 2007). PCBs and PFASs also have over-activated liver and intestinal nuclear receptors, including pregnane X receptor (PXR) and constitutive androstane receptor (CAR), in *in vitro* studies (Kamata et al. 2015, Dingermans et al. 2016). PXR and CAR over-activation by exogenous compounds have been associated with hyperglycemia (Banerjee et al. 2015). Despite these proposed mechanisms identifying PFASs as metabolic disruptors, the inverse associations seen with all PFASs were unexpected. Given our limited statistical power, an investigation with a more robust sample size, particularly among overweight and obese pregnant women, may help elucidate these findings. Further, future studies should investigate potential racial/ethnic differences of PFASs and metabolic disruption since evidence has suggested differences by race/ethnicity (Gaston et al. 2020).

Pregnancy is both a sensitive window of exposure and an increasingly insulin resistant state in women. Further perturbation due to environmental chemical exposures may permanently alter pancreatic beta cell functioning (Sargis and Simmons 2019), and, therefore, is a potentially unique period of susceptibility for metabolic disrupting chemicals. Our use of intermediate glycemic biomarkers of cardiometabolic health, including glucose, insulin and HOMA-IR, may allow for more sensitive predictors of the impact of POPs; more studies should consider inclusion of these outcome biomarkers to confirm their utility.

Our diverse study population consisting of underrepresented minorities and low-income pregnant women may bear a disproportionate risk for environmental chemical exposures and glycemic dysfunction. An updated review of epidemiological studies of cardiometabolic health among vulnerable populations from 2018–2019 found certain POPs, including PFASs, were associated with both an increased risk in GDM and abnormal glucose regulation (Gaston et al. 2020). Ruiz et al. (2018) hypothesized that higher exposure to diabetogenic chemicals, including PCBs, disproportionately impacts African Americans, Latinos, and low-income populations, leading to a higher risk of developing diabetes. Further research among these specific populations during pregnancy is needed to explain these potential disparities.

Our study was limited by its cross-sectional study design; thus, temporality cannot be adequately assessed. Furthermore, the possibility of reverse causation cannot be ruled out. For example, it is possible that abnormal glycemic functioning and high adiposity in our study population may, in turn, increase uptake and accumulation of lipophilic POPs. To avoid the potential for reverse causality, future investigations should employ a prospective study design. Our relatively small sample size of 95 women may have hindered our ability to conduct subsample analyses. We were unable to evaluate data involved in the screening and diagnosis of GDM in our study population; rather, we used glycemic measures reflective of one's basal metabolic rate. Still, these measures may be informative to GDM. Studies examining early fasting glucose concentrations prior to 24 weeks gestation have found it a useful predictor of GDM risk (Smirnakis et al. 2005; Riskin-Mashiah et a. 2009; Harrison et al. 2015), and it has been proposed that a fasting glucose of ≥ 5.1 mmol/L before 24 weeks be used as the first pass early screening tool for dysglycemia during pregnancy (Cosson et al. 2017). Our summary measures by chemical class allowed us to examine the class-specific

burden regardless of the contribution of each individual chemical; however, we do note that this method may be driven by chemicals with higher absolute concentrations. While BKMR allowed us to identify relevant chemicals important to the chemical mixture, our limited sample size may have inhibited our ability to evaluate non-linearities and interactions. Additionally, the results from this population of overweight women limits generalizability to pregnant women with normal prepregnancy weight. Lastly, the timing of maternal exposure to POPs are unknown due to single-spot measurements taken in mostly second-trimester pregnancy.

There were several strengths to our study. We were able to examine a population that is typically under-sampled in environmental epidemiologic studies: pregnant women who were overweight and obese, low-income, and women of color. Given that over half of US pregnant women are overweight or obese before pregnancy (Deputy et al. 2018), 42% of deliveries are Medicaid financed (Martin et al. 2019), and almost half of women who give birth are a non-white race or ethnicity, greater efforts should be made to account for these understudied populations. Furthermore, we were able to analyze data from a group of women who are at a higher risk of glycemic outcomes, given high adiposity. We also included concurrent data from multiple chemical classes, including OH-PBDEs which are rarely included. Despite our limited sample size, we were able to correct for potential multicollinearity and assess for variable selection using an increasingly popular mixtures method. Additionally, we were able to assess multiple continuous outcome measures of basal glycemic functioning.

In conclusion, we found variability in the direction and magnitude of the association within and across four POPs chemical classes and biochemical indicators of dysglycemia during pregnancy in a diverse group of overweight and obese pregnant women. Future studies with a larger sample size may serve to further confirm our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank Irene Headen for her help in formulating our research plan, and Susanna Mitro and Ruth Geller for their assistance with data management and analyses.

This research was support by the National Institutes of Health grants (NHLBI U01 HL097973, NIEHS R01ES026166, NIEHS R00ES019881).

6. References

Baccarelli A, Pfeiffer R, Consonni D, Pesatori AC, Bonzini M, Patterson DG Jr, Bertazzi PA, Landi MT. 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. [PubMed: 15992596]

Baker NA, Shoemaker R, English V, Larian N, Sunkara M, Morris AJ, et al. 2015 Effects of adipocyte aryl hydrocarbon receptor deficiency on PCB-induced disruption of glucose homeostasis in lean and obese mice. Environ Health Perspect Oct;123(10):944–50.

Banerjee M, Robbins D, Chen T. 2015 Targeting xenobiotic receptors PXR and CAR in human diseases. Drug Discov Today 20(5):618–628. [PubMed: 25463033]

Barrett HL, Dekker Nitert M, McIntyre HD, Callaway LK. 2014 Normalizing metabolism in diabetic pregnancy: Is it time to target lipids? Diabetes Care 37(5):1484–1493. [PubMed: 24757231]

Bickel G, Price C, Hamilton W, & Cook J (2000). Guide to measuring household food security, revised 2000. USDA Food and Nutrition Service: Alexandria, VA.

Bobb JF, Henn BC, Valeri L, Coull BA. 2018 Statistical software for analyzing the health effects of multiple concurrent exposures via bayesian kernel machine regression. Environ Health 17(1):1–10. [PubMed: 29301538]

Bobb JF, Valeri L, Claus Henn B, Christiani DC, Wright RO, Mazumdar M et al. 2015 Bayesian kernel machine regression for estimating the health effects of multi-pollutant mixtures. Biostatistics 16(3):493–508. [PubMed: 25532525]

Casals-Casas C, Desvergne B. 2011 Endocrine disruptors: From endocrine to metabolic disruption. Annu Rev Physiol 73:135–162. [PubMed: 21054169]

Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, Dietz PM. 2007 Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care; 30(8):2070–6. [PubMed: 17416786]

Coleman-Phox K, Laraia BA, 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 10:10.5888/pcd10.120096; doi: 10.5888/pcd10.120096 [doi].

Cosson E, Carbillon L, Valensi P. 2017 High fasting plasma glucose during early pregnancy: a review about early gestational diabetes mellitus. Journal of diabetes research 2017:8921712. [PubMed: 29181414]

Deputy NP, Dub B, Sharma AJ. 2018 Prevalence and trends in prepregnancy normal weight — 48 States, New York City, and District of Columbia, 2011–2015. MMWR Morb Mortal Wkly Rep;66:1402–1407. [PubMed: 29300720]

Diamanti-Kandarakis E, Bourguignon J, Giudice LC, Hauser R, Prins GS, Soto AM et al. 2009 Endocrine-disrupting chemicals: An endocrine society scientific statement. Endocr Rev 30(4):293–342. [PubMed: 19502515]

Dingemans MM, Kock M, van den Berg M. 2016 Mechanisms of action point towards combined PBDE/NDL-PCB risk assessment. Toxicological Sciences 153(2):215–224. [PubMed: 27672163]

Eslami B, Naddafi K, Rastkari N, Rashidi BH, Djazayeri A, Malekafzali H. 2016 Association between serum concentrations of persistent organic pollutants and gestational diabetes mellitus in primiparous women. Envir Res 151:706–712.

Gaston SA, Birnbaum LS, Jackson CL. 2020 Synthetic chemicals and cardiometabolic health across the life course among vulnerable populations: A review of the literature from 2018 to 2019. Current Environmental Health Reports 7(1):30–47. [PubMed: 32037478]

Gray SL, Shaw AC, Gagne AX, Chan HM. 2013 Chronic exposure to PCBs (Aroclor 1254) exacerbates obesity-induced insulin resistance and hyperinsulinemia in mice. Journal of Toxicology and Environmental Health, Part A 76(12):701–715. [PubMed: 23980837]

Harmon KA, Gerard L, Jensen DR, Kealey EH, Hernandez TL, Reece MS et al. 2011 Continuous glucose profiles in obese and normal-weight pregnant women on a controlled diet: Metabolic determinants of fetal growth. Diabetes Care 34(10):2198–2204. [PubMed: 21775754]

Harrison CL, Lombard CB, East C, Boyle J, Teede HJ. 2015 Risk stratification in early pregnancy for women at increased risk of gestational diabetes. Diabetes Research and Clinical Practice 107(1):61–8. [PubMed: 25444356]

Helsel DR. 1990 Less than obvious-statistical treatment of data below the detection limit. Environ Sci Technol 24(12):1766–74.

Hovander L, Athanasiadou M, Asplund L, Jensen S, Wehler EK. 2000 Extraction and cleanup methods for analysis of phenolic and neutral organohalogens in plasma. J Anal Toxicol 24(8):696–703. [PubMed: 11110024]

Hunt KJ, Schuller KL. 2007 The increasing prevalence of diabetes in pregnancy. Obstet Gynecol Clin North Am 34(2):173–199. [PubMed: 17572266]

Jaacks LM, Barr DB, Sundaram R, Maisog JM, Zhang C, Louis GM. 2016 Pre-pregnancy maternal exposure to polybrominated and polychlorinated biphenyls and gestational diabetes: a prospective cohort study. Environmental Health 15(1):11. [PubMed: 26792546]

Kamata R, Shiraishi F, Kageyama S, Nakajima D. 2015 Detection and measurement of the agonistic activities of PCBs and mono-hydroxylated PCBs to the constitutive androstane receptor using a recombinant yeast assay. Toxicology in Vitro 29(7):1859–1867. [PubMed: 26231822]

Lavery J, Friedman A, Keyes K, Wright J, Ananth C. 2017 Gestational diabetes in the United States: Temporal changes in prevalence rates between 1979 and 2010. BJOG: An International Journal of Obstetrics & Gynaecology 124(5):804–813. [PubMed: 27510598]

Levy JC, Matthews DR, Hermans MP. 1998 Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care 21(12):2191–2192; doi: 10.2337/diacare.21.12.2191 [doi]. [PubMed: 9839117]

Liu X, Zhang L, Li J, et al. 2018 A nested case-control study of the association between exposure to polybrominated diphenyl ethers and the risk of gestational diabetes mellitus. Environ Int 119:232–238. [PubMed: 29980046]

Liu X, Zhang L, Chen L, Li J, Wang Y, Wang J et al. 2019 Structure-based investigation on the association between perfluoroalkyl acids exposure and both gestational diabetes mellitus and glucose homeostasis in pregnant women. Environ Int 127:85–93. [PubMed: 30909097]

Lowe WL, Scholtens DM, Kuang A, Linder B, Lawrence JM, Lebenthal Y, et al. 2019 Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): Maternal gestational diabetes mellitus and childhood glucose metabolism. Diabetes Care 1;42(3):372–80.

Martin JA, Hamilton BE, Osterman MJ, Driscoll AK. 2019 Births: Final data for 2018. National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System 68(13):1–47.

Matilla-Santander N, Valvi D, Lopez-Espinosa MJ, Manzano-Salgado CB, Ballester F, Ibarluzea J, et al. 2017 Exposure to perfluoroalkyl substances and metabolic outcomes in pregnant women: evidence from the Spanish INMA birth cohorts. Environmental Health Perspectives 125(11):117004. [PubMed: 29135438]

Mehta SS, Applebaum KM, James-Todd T, Coleman-Phox K, Adler N, Laraia B et al. 2020 Associations between sociodemographic characteristics and exposures to PBDEs, OH-PBDEs, PCBs, and PFASs in a diverse, overweight population of pregnant women. Journal of Exposure Science and Environmental Epidemiology 30(1):42–55. [PubMed: 31548625]

Parry E, Zota AR, Park J, Woodruff TJ. Polybrominated diphenyl ethers (PBDEs) and hydroxylated PBDE metabolites (OH-PBDEs): A six-year temporal trend in Northern California pregnant women. Chemosphere 2018;195:777–783. [PubMed: 29289024]

Phillips DL, Pirkle JL, Burse VW, Bernert JT, Henderson LO, Needham LL. 1989 Chlorinated hydrocarbon levels in human serum: Effects of fasting and feeding. Arch Environ Contam Toxicol 18(4):495–500. [PubMed: 2505694]

Preston EV, Rifas-Shiman SL, Hivert MF, Zota AR, Sagiv SK, Calafat AM, Oken E, James-Todd T. 2020 Associations of per-and polyfluoroalkyl substances (PFAS) with glucose tolerance during pregnancy in Project Viva. The Journal of Clinical Endocrinology and Metabolism 105(8).

Rahman ML, Zhang C, Smarr MM, Lee S, Honda M, Kannan K et al. 2019 Persistent organic pollutants and gestational diabetes: A multi-center prospective cohort study of healthy US women. Environ Int 124:249–258. [PubMed: 30660025]

Remillard RB, Bunce NJ. 2002 Linking dioxins to diabetes: epidemiology and biologic plausibility. Environmental Health Perspectives 110(9):853–8. [PubMed: 12204817]

Riskin-Mashiah S, Younes G, Damti A, Auslender R. 2009 First-trimester fasting hyperglycemia and adverse pregnancy outcomes. Diabetes Care 32(9):1639–43. [PubMed: 19549728]

Ruiz D, Becerra M, Jagai JS, Ard K, Sargis RM. 2018 Disparities in environmental exposures to endocrine-disrupting chemicals and diabetes risk in vulnerable populations. Diabetes Care 41(1):193–205. [PubMed: 29142003]

Sargis RM, Simmons RA. 2019 Environmental neglect: endocrine disruptors as underappreciated but potentially modifiable diabetes risk factors. Diabetologia 27:1–2.

Scholtens DM, Kuang A, Lowe LP, Hamilton J, Lawrence JM, Lebenthal Y, et al. 2019 Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): Maternal glycemia and childhood glucose metabolism. Diabetes Care 42(3):381–92. [PubMed: 30617141]

Shapiro GD, Dodds L, Arbuckle TE, Ashley-Martin J, Ettinger AS, Fisher M et al. 2016 Exposure to organophosphorus and organochlorine pesticides, perfluoroalkyl substances, and polychlorinated biphenyls in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: The MIREC study. Environ Res 147:71–81. [PubMed: 26852007]

Smarr MM, Grantz KL, Zhang C, Sundaram R, Maisog JM, Barr DB et al. 2016 Persistent organic pollutants and pregnancy complications. Sci Total Environ 551:285–291. [PubMed: 26878640]

Smirnakis KV, Martinez A, Blatman KH, Wolf M, Ecker JL, Thadhani R. 2005 Early pregnancy insulin resistance and subsequent gestational diabetes mellitus. Diabetes Care 28(5):1207–8. [PubMed: 15855591]

Takacs ML, Abbott BD. 2007 Activation of mouse and human peroxisome proliferator–activated receptors (α, β/δ, γ) by perfluorooctanoic acid and perfluorooctane sulfonate. Toxicological Sciences 95(1):108–117. [PubMed: 17047030]

Vafeiadi M, Roumeliotaki T, Chalkiadaki G, Rantakokko P, Kiviranta H, Fthenou E et al. 2017 Persistent organic pollutants in early pregnancy and risk of gestational diabetes mellitus. Environ Int 98:89–95. [PubMed: 27743729]

Valvi D, Oulhote Y, Weihe P, Dalgård C, Bjerve KS, Steuerwald U et al. 2017 Gestational diabetes and offspring birth size at elevated environmental pollutant exposures. Environ Int 107:205–215. [PubMed: 28753482]

Vieten C, Laraia BA, Kristeller J, Adler N, Coleman-Phox K, Bush NR et al. 2018 The mindful moms training: Development of a mindfulness-based intervention to reduce stress and overeating during pregnancy. BMC pregnancy and childbirth 18(1):201. [PubMed: 29859038]

Wang H, Yang J, Du H, Xu L, Liu S, Yi J, Qian X, Chen Y, Jiang Q, He G. 2018 Perfluoroalkyl substances, glucose homeostasis, and gestational diabetes mellitus in Chinese pregnant women: A repeat measurement-based prospective study. Environ Int 114:12–20. [PubMed: 29459131]

Wahlang B, Falkner KC, Gregory B, Ansert D, Young D, Conklin DJ et al. 2013 Polychlorinated biphenyl 153 is a diet-dependent obesogen that worsens nonalcoholic fatty liver disease in male C57BL6/J mice. J Nutr Biochem 24(9):1587–1595. [PubMed: 23618531]

Woodruff TJ, Zota AR, Schwartz JM. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. Environ Health Perspect 2011;119(6):878. [PubMed: 21233055]

Xiong X, Saunders L, Wang F, Demianczuk N. 2001 Gestational diabetes mellitus: Prevalence, risk factors, maternal and infant outcomes. International Journal of Gynecology & Obstetrics 75(3):221–228. [PubMed: 11728481]

Zhang C, Sundaram R, Maisog J, Calafat AM, Barr DB, Louis GMB. 2015 A prospective study of prepregnancy serum concentrations of perfluorochemicals and the risk of gestational diabetes. Fertil Steril 103(1):184–189. [PubMed: 25450302]

Zhang L, Liu X, Meng G, Chi M, Li J, Yin S, Zhao Y, Wu Y. 2018 Non-dioxin-like polychlorinated biphenyls in early pregnancy and risk of gestational diabetes mellitus. Environ Int 115:127–32. [PubMed: 29558635]

Zota AR, Park JS, Wang Y, Petreas M, Zoeller RT, Woodruff TJ. 2011 Polybrominated diphenyl ethers, hydroxylated polybrominated diphenyl ethers, and measures of thyroid function in second trimester pregnant women in California. Environ Sci Technol 45(18):7896–905. [PubMed: 21830753]

Zota AR, Geller RJ, Romano LE, Coleman-Phox K, Adler NE, Parry E et al. 2018 Association between persistent endocrine-disrupting chemicals (PBDEs, OH-PBDEs, PCBs, and PFASs) and biomarkers of inflammation and cellular aging during pregnancy and postpartum. Environ Int 115:9–20. [PubMed: 29533840]

Highlights

- Minorities, low income, and overweight/obese pregnant women remain poorly studied
- Maternal PCBs were associated with higher glucose, insulin, and insulin resistance
- PFASs, most PBDEs/OH-PBDEs were inversely associated with glycemic indicators
- Future studies on POPs exposure on maternal cardiometabolic health is warranted

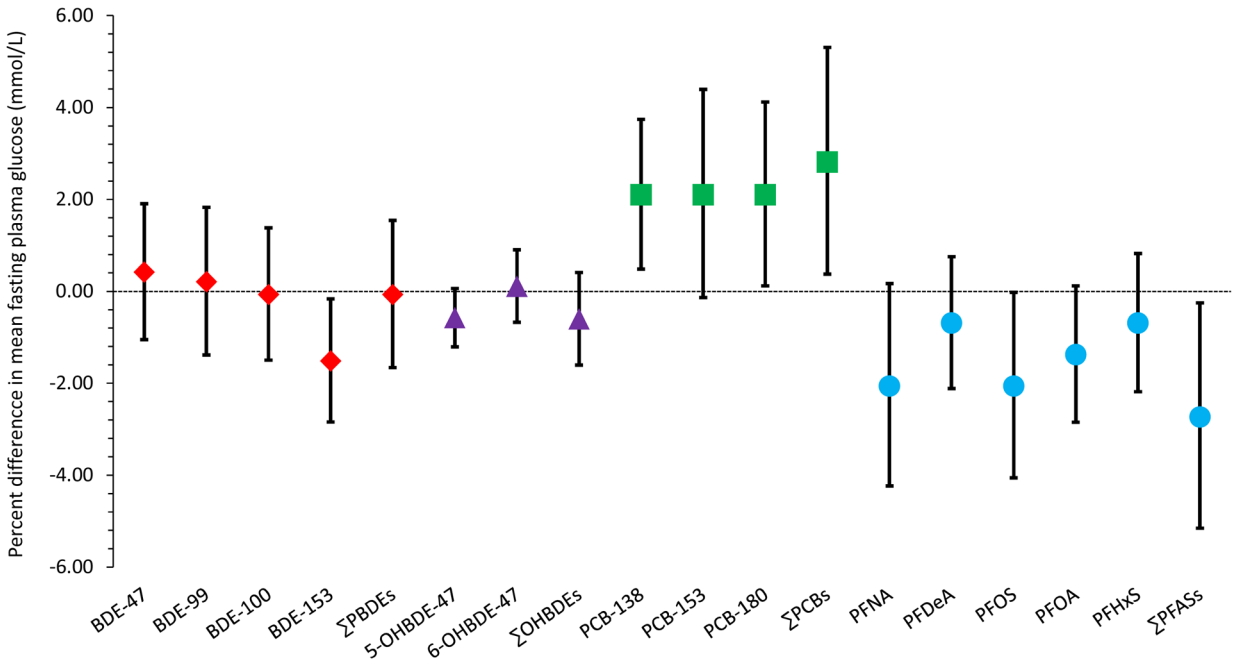

Figure 1.

Percent difference in maternal fasting plasma glucose associated with a doubling of individual and aggregate maternal serum concentrations of PBDEs, OH-PBDEs, PCBs, and PFASs, after controlling for covariates (N=95)[1].

[1]Final models adjusted for maternal age at enrollment, race/ethnicity, pre-pregnancy BMI (kg/m^2), parity, and household income.

Note: Red diamonds = PBDEs; Purple triangles = OH-PBDEs; Green squares = PCBs; Blue circles = PFASs.

Table 1.

Maternal serum concentrations of PBDEs, OH-PBDEs, PCBs, and PFASs at baseline (N=95).

Analyte/Congener		% >MDL	GM (GSE)
PBDE, ng/g lipid	BDE-47	100.0	33.20 (2.88)
	BDE-99	89.5	8.42 (0.67)
	BDE-100	81.1	5.19 (0.48)
	BDE-153	92.6	9.15 (0.85)
	ΣPBDEs		59.53 (4.77)
OH-PBDE, ng/mL	5-OHBDE-47	50.0	0.004 (0.001)
	6-OHBDE-47	55.8	0.004 (0.001)
	ΣOHBDEs	---	0.01 (0.002)
PCB, ng/g lipid	PCB-138	59.0	2.36 (0.22)
	PCB-153	87.5	4.02 (0.26)
	PCB-180	59.0	2.12 (0.18)
	ΣPCBs	---	9.08 (0.62)
PFAS, ng/mL	PFNA	100.0	0.57 (0.03)
	PFDeA	69.5	0.17 (0.01)
	PFOS	100.0	2.86 (0.17)
	PFOA	97.9	1.19 (0.09)
	PFHxS	99.0	0.53 (0.04)
	ΣPFASs	---	5.81 (0.27)

Abbreviations: GM = geometric mean; GSE = geometric standard error of the mean; MDL = methodological detection limit.

Table 2.

Maternal fasting plasma glucose, fasting plasma insulin, and insulin resistance by select participant characteristics.

			Fasting glucose, mmol/L	Fasting insulin, pmol/L	HOMA-IR, units
Characteristics		**N (%)**	**GM (GSE)**	**GM (GSE)**	**GM (GSE)**
Total study population		95 (100.00)	4.42 (0.04)	81.19 (4.73)	1.65 (0.09)
Race/ethnicity	Non-Hispanic White	34 (35.80)	4.45 (0.06)	77.63 (7.27)	1.58 (0.15)
	Non-Hispanic Black	33 (34.70)	4.41 (0.07)	92.68 (9.66)	1.85 (0.19)
	Latina	28 (29.47)	4.40 (0.07)	73.36 (7.31)	1.50 (0.15)
Maternal age at enrollment	≤ 27 years	48 (50.53)	4.33 (0.06)	91.78 (7.03)	1.84 (0.14)
	> 27 years	47 (49.47)	4.52 (0.05)	71.64 (6.04)	1.47 (0.12)
Household income[1]	≤ poverty level	43 (45.26)	4.46 (0.07)	84.36 (7.79)	1.72 (0.15)
	> poverty level	52 (54.74)	4.39 (0.05)	78.66 (5.82)	1.59 (0.12)
Education beyond high school	No	32 (33.68)	4.40 (0.07)	91.02 (9.03)	1.82 (0.17)
	Yes	63 (66.32)	4.43 (0.05)	76.61 (5.43)	1.57 (0.11)
Food security[2]	Marginal/high	54 (58.70)	4.45 (0.05)	86.21 (6.86)	1.74 (0.14)
	Low/very low	38 (41.30)	4.37 (0.06)	73.37 (6.37)	1.49 (0.13)
Gestational age[3]	< 14 weeks	26 (27.37)	4.42 (0.08)	78.04 (7.25)	1.59 (0.14)
	≥ 14 weeks	69 (72.63)	4.42 (0.05)	82.41 (5.95)	1.67 (0.12)
BMI[4]	< 30 kg/m^2	48 (50.53)	4.33 (0.06)	63.81 (5.15)	1.30 (0.11)
	≥ 30 kg/m^2	47 (49.47)	4.49 (0.05)	96.74 (7.08)	1.95 (0.14)
Parity	Nulliparous	47 (49.47)	4.44 (0.07)	91.54 (7.72)	1.86 (0.16)
	Multiparous	48 (50.53)	4.40 (0.04)	72.20 (5.55)	1.46 (0.11)

[1] Poverty level is categorized relative to 100% of the 2011 Federal poverty level.

[2] N=3 missing data on food security.

[3] Measured at baseline (range: 10–24 weeks gestation).

[4] 91 self-reported pre-pregnancy BMI that were later confirmed with medical records, and 4 missing pre-pregnancy BMI were imputed using BMI at baseline.

Abbreviations: GM = geometric mean; GSE = geometric standard error of the mean; BMI = body mass index; HOMA-IR = homeostatic model assessment of insulin resistance.

Table 3.

Group and conditional posterior inclusion probabilities (PIPs) for maternal serum concentrations of PBDEs/OH-PBDEs, PCBs, and PFASs and fasting plasma glucose using BKMR.

POP	Group #	Group PIP[1]	Conditional PIP[2]
BDE-47	1	0.67	0.06
BDE-99	1	0.67	0.07
BDE-100	1	0.67	0.09
BDE-153	1	0.67	0.39
5-OHBDE-47	1	0.67	0.30
6-OHBDE-47	1	0.67	0.08
PCB-138	2	0.70	0.32
PCB-153	2	0. 70	0.39
PCB-180	2	0. 70	0.29
PFNA	3	0.79	0.58
PFDeA	3	0.79	0.06
PFOS	3	0.79	0.20
PFOA	3	0.79	0.11
PFHxS	3	0.79	0.05

[1]Group posterior inclusion probabilities are the likelihood that a group was included in the model based on 50,000 iterations of the Markov Chain Monte Carlo algorithm.

[2]Conditional PIPs are the likelihood that a particular chemical was included in the model, conditional on the group being included in the model.

Note: All models adjusted for maternal age at enrollment, gestational age at baseline, race/ethnicity, pre-pregnancy BMI (kg/m^2), parity, and household income.