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Persistent organic pollutants and gestational diabetes: A multi-center prospective cohort study of healthy US women

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ABSTRACT

Background: Persistent organic pollutants (POPs) are linked with insulin resistance and type-2 diabetes (T2D) in the general population. However, their associations with gestational diabetes (GDM) are inconsistent.
Objective: We prospectively evaluated the associations of POPs measured in early pregnancy with GDM risk. We also assessed whether pre-pregnancy BMI (ppBMI) and family history of T2D modify this risk.
Methods: In NICHD Fetal Growth Study, Singletons, we measured plasma concentration of 76 POPs, including 11 organochlorine pesticides (OCPs), 9 polybrominated diphenylethers (PBDEs), 44 polychlorinated biphenyls (PCBs), and 11 *per*-and polyfluoroalkyl substances (PFAS) among 2334 healthy non-obese women at 8–13 weeks of gestation. GDM was diagnosed by Carpenter and Coustan criteria. We constructed chemical networks using a weighted-correlation algorithm and examined the associations of individual chemical and chemical networks with GDM using multivariate Poisson regression with robust variance.
Results: Higher concentrations of PCBs with six or more chlorine atoms were associated with increased risk of GDM in the overall cohort (risk ratios [RRs] range: 1.08–1.13 per 1-standard deviation [SD] increment) and among women with a family history of T2D (RRs range: 1.08–1.48 per 1-SD increment) or normal ppBMI (RRs range: 1.08–1.22 per 1-SD increment). Similar associations were observed for the chemical network comprised of PCBs with ≥6 chlorine atoms and the summary measure of total PCBs and non-dioxin like PCBs (138, 153, 170, 180). Furthermore, four PFAS congeners - perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFOA), perfluoroheptanoic acid (PFHpA), and perfluorododecanoic acid (PFDoDA) - showed significant positive associations with GDM among women with a family history of T2D (RRs range:1.22–3.18 per 1-SD increment), whereas BDE47 and BDE153 showed significant positive associations among women without a family history of T2D.
Conclusions: Environmentally relevant levels of heavily chlorinated PCBs and some PFAS and PBDEs were positively associated with GDM with suggestive effect modifications by family history of T2D and body adiposity status.

Abbreviations: POPs, Persistent Organic Pollutants; GDM, Gestational Diabetes Mellitus; T2D, type 2 diabetes; ppBMI, pre-pregnancy BMI; OCPs, Organochlorine pesticides; PBDEs, Polybrominated diphenylethers; PBB, Polybrominated biphenyl; PCBs, Polychlorinated biphenyls; PFAS, Per-and polyfluoroalkyl substances; PFNA, Perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFHpA, Perfluoroheptanoic acid; PFDoDA, Perfluorododecanoic acid; N-MeFOSAA, *N*-methylperfluoro-1-octanesulfonamidoacetic acid; PFDA, Perfluorodecanoic acid; PFDS, Perfluorodecane sulfonate; PFHxS, Perfluorohexanesulfonic acid; PFOS, Perfluorooctanesulfonic acid; PFOSA, Perfluorooctane sulfonamide; PFUnDA, Perfluoroundecanoic acid; HCB, hexachlorobenzene; β-HCH, beta-hexachlorocyclohexane; ϒ-HCH, gamma-hexachlorocyclohexane; *p,p′-DDE*, *p,p′*-dichlorodiphenyldichloroethylene; *o,p′*-DDD, *o,p′*-dichlorodiphenyldichloroethane; *P,P′*-DDT, *p,p′*-dichlorodiphenyldichloroethane; [*p,p′*-DDD], *p,p′*-dichlorodiphenyltrichloroethane

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1. Background

Persistent organic pollutants (POPs) are a group of lipophilic chemicals that are resistant to environmental degradation and can bioaccumulate and biomagnify within the food chain (Porta et al., 2008). Examples of POPs include organochlorine pesticides (OCPs), polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), and *per*- and polyfluoroalkyl substances (PFAS). POPs were widely used through most of the 20th century. The production and use of most POPs are currently banned or restricted under the Stockholm Convention (Stockholm Convention on Persistent Organic Pollutants, 2009). Yet, POPs are ubiquitously detected in the environment, mainly because of their long half-lives. Population exposure to POPs primarily occurs through consumption of contaminated food and drinking water (Fisher, 1999). Once ingested, POPs are stored in the adipose tissue (La Merrill et al., 2013), acting as the source of long-term internal exposure (La Merrill et al., 2013). Therefore, it is of significant public health interest to examine the population health effect of POPs at an environmentally relevant level, especially among the pregnant population.

Gestational diabetes (GDM), defined as impaired glucose tolerance with onset or first recognition during pregnancy, is one of the most common pregnancy complications (Hartling et al., 2012), which affect 5.7% - 8.7% of all pregnancies in the United States (DeSisto et al., 2014). GDM has been linked with both short- and long-term adverse health consequences for the mother and offspring. Women themselves are at 4.8–11.5 times increased risk of developing type 2 diabetes (T2D) later in life (Bellamy et al., 2009). Offspring are more likely to be macrosomic at birth and are at a higher risk of developing glucose intolerance in the adulthood (American Diabetes Association, 2004). More alarmingly, the prevalence of GDM is escalating around the world (Zhu and Zhang, 2016), which is believed to be precipitated by the epidemics in obesity and T2D (Lee et al., 2014). Both obesity and family history of T2D are important predictors of GDM (Savvidou et al., 2010); they are also suspected to modify the effect of POPs on metabolic dysfunction (Lee, 2012; Franks, 2011).

Exposure to POPs of various classes has been associated with endocrine and metabolic disorders such as obesity, (Lee et al., 2011a; Tang-Peronard et al., 2011), insulin resistance (Lee et al., 2011a; Cardenas et al., 2017; Lee et al., 2007a), impaired glucose tolerance (Kuo et al., 2013; Wan et al., 2014), and T2D (Lee et al., 2014; Magliano et al., 2014; Taylor et al., 2013) in the general population. However, epidemiological evidence for an association between POPs and GDM is inconsistent. While most studies concluded that some POPs or some combinations of POPs are associated with GDM, no single class of POPs showed a consistent association. For instance, significant positive associations between PCBs and GDM were reported in the Rhea pregnancy cohort in Greece (Vafeiadi et al., 2017), while null associations were reported in the Canadian MIREC birth cohort (Shapiro et al., 2016) and inverse associations in the US LIFE Study cohort (Jaacks et al., 2016). Associations for PBDEs and PFAS with GDM are also inconsistent (Shapiro et al., 2016; Smarr et al., 2016; Valvi et al., 2017; Zhang et al., 2015; Liu et al., 2018), whereas most studies reported null associations for OCPs (Vafeiadi et al., 2017; Shapiro et al., 2016; Smarr et al., 2016; Valvi et al., 2017). Furthermore, most of these studies did not account for women's family history of diabetes, resulting in potential residual confounding in their estimates. Moreover, despite the fact that POPs are highly correlated, previous studies examined these chemicals either individually or using a summary measure of some combination of POPs without taking into account the inherent correlation among these chemicals.

In the current study, we aimed to prospectively evaluate the associations of early pregnancy plasma concentrations of POPs and POP mixtures with GDM risk among US pregnant women with low-risk antenatal profiles. We also sought to evaluate whether women's pre-pregnancy body mass index (ppBMI) and family history of T2D modify this risk.

2. Methods

2.1. Study population

The NICHD Fetal Growth Study, Singletons is a multicenter, multiethnic prospective cohort study of pregnant women with low-risk antenatal profiles. The study was conducted between July 2009 to January 2013 with the participation of 12 clinical sites located in New York (2), New Jersey (1), Delaware (1), Rhode Island (1), Massachusetts (1), South Carolina (1), Alabama (1), Illinois (1), and California (3). Details of the study were previously described (Grewal et al., 2018). Briefly, research nurses approached women aged 18–40 years who presented for their first prenatal visit to a participating clinical site at < 13 weeks of gestation. A screening ultrasound was performed between 10 and 13 weeks to confirm gestational age. Last menstruation period dates were matched by ultrasound within 5 days for gestation estimates between 8w0d and 10w6d, 6 days for estimates between 11w0d and 12w6d, and 7 days for estimates between 13w0d and 13w6d. A total of 2802 woman with an ultrasound confirmed viable singleton pregnancy between 8w0d to 13w6d without a major pre-existing medical condition was recruited in the study. This analysis included 2334 low-risk women with a ppBMI within the normal or overweight range (BMI 19.0–29.9 kg/m^2) and who had available chemical exposure data. POPs were not measured among obese women (BMI ≥ 30 kg/m^2; n = 468); hence, those women were excluded from this analysis.

2.2. Data collection

The study was approved by the institutional review boards of all participating sites. All participants provided written informed consent before data collection. Upon recruitment, women were randomized to one of four groups and underwent five in-hospital follow-up visits at targeted gestational weeks 16–22, 24–29, 30–33, 34–37, and 38–41 (Grewal et al., 2018). At each visit, an interview was conducted using a standardized and structured questionnaire to collect information on women's demographic characteristics, lifestyle, and reproductive and pregnancy history. Trained research assistants collected women's anthropometric measurements and venous blood samples longitudinally at the baseline and during each study visit. Plasma samples were processed immediately after blood collection and stored at −80°C until analysis.

All women underwent standard clinical care that included a glucose challenge test and/or an oral glucose tolerance test (OGTT). All women underwent a 100 g 3-h OGTT test except for 123 participants who underwent a 75 g 2-h OGTT test. OGTT tests were performed at a mean (± standard deviation) gestational age of 27.5 (± 4.3) weeks. GDM was diagnosed by medical records review of the OGTT test results. Based on the recommendations of the American College of Obstetrics and Gynecologists (Committee on Practice Bulletins-Obstetrics, 2013), we classified GDM using the Carpenter and Coustan criteria of at least two diagnostic plasma glucose measurements at or above the defined thresholds: fasting, 5.3 mmol/L; 1-h, 10.0 mmol/L; 2-h, 8.6 mmol/L; and 3-h, 7.8 mmol/L. The same thresholds for fasting, 1-h, and 2-h glucose measurements were applied for women who underwent the 75 g 2-h OGTT test for consistency.

2.3. Laboratory analysis

Chemical analysis was performed by the Wadsworth Center, New York State Department of Health. Plasma concentrations of 76 chemicals were measured following standardized procedure (Ma et al., 2014; Kannan et al., 2004). These chemicals included: 11 organochlorine pesticides (OCPs) (beta-hexachlorocyclohexane [β-HCH], gamma-hexachlorocyclohexane [ϒ-HCH], hexachlorobenzene [HCB], Oxychlordane, trans-chlordane, trans-nonachlor, *p,p′*-dichlorodiphenyldichloroethylene [*p,p′*-DDE], *o,p′*-

dichlorodiphenyldichloroethane [*o,p'*-DDD], *p,p'*-dichlorodiphenyldichloroethane [*p,p'*-DDD], *p,p'*- dichlorodiphenyltrichloroethane [*P,P'*-DDT], and mirex); 1 polybrominated biphenyl (PBB 153) and 9 polybrominated diphenyl ethers (PBDE 28, 47, 85, 99, 100, 153, 154, 183, 209); 44 polychlorinated biphenyls (PCB 5_8, 18_17, 22, 31_28, 33_20, 37, 41_64, 44, 47_48_75, 49_43, 52_73, 66_80, 70_76, 74_61, B90_101_89, 93_95, 99, 85_120, 110, 118_106, 105_127, 114_122, 128, 137, 138_158, 146_161, 153, 156, 157, 167, 170, 172_192, 177, 180, 182_187, 183, 194, 195, 196_203, 199, 202, 206, 208, and 209); and 11 poly-and-perfluorinated alkyl substances (PFAS) (*N*-methylperfluoro-1-octanesulfonamidoacetic acid [N-MeFOSAA], perfluorodecanoic acid [PFDA], perfluorododecanoic acid [PFDoDA], perfluorodecane sulfonate [PFDS], perfluoroheptanoic acid [PFHpA], perfluorohexanesulfonic acid [PFHxS], perfluorononanoic acid [PFNA], perfluorooctanoic acid [PFOA], perfluorooctanesulfonic acid [PFOS], perfluorooctane sulfonamide [PFOSA], and perfluoroundecanoic acid [PFUnDA]). The quantification of OCPs, PBDEs, and PCBs was based on an isotope dilution method (Ma et al., 2014; Kannan et al., 2004). Two procedural blanks and SRM1958 were analyzed for every 27 samples. OCPs were analyzed using a Thermo Finnigan (Bremen, Germany) Trace GC Ultra coupled with a double focusing sector mass spectrometer (DFS). PBDEs were analyzed using a gas chromatograph (GC 7890A, Agilent Technologies, Atlanta, GA) coupled with a mass spectrometer (MSD 5975), while PCBs were analyzed by a JEOL (Tokyo, Japan) UltraFocus high-resolution mass spectrometer (JMS-800D) and PFAS were analyzed using ultra-performance liquid chromatography (Acquity I Class; Waters, Milford, MA, US) coupled with an electrospray triple quadrupole tandem mass spectrometry (API 5500; AB SCIEX, Framingham, MA, US) (Ma et al., 2014; Kannan et al., 2004).

All chemical concentrations were reported on a volume basis and expressed in ng/ml serum. Machine-observed values for all chemical concentrations, including concentrations below the level of quantifications (LOQs) were used in analysis (Schisterman et al., 2006; Lubin et al., 2004). The LOQs varied by analytes, ranging between 0.0025 – 0.005 ng/mL for both OCPs and PBDEs, 0.005 ng/mL for PCBs, and 0.02–0.06 ng/mL for PFAS. Plasma lipids were quantified using commercially available enzymatic methods (Akins et al., 1989). Plasma total lipids were calculated based on individual components using the following equation: plasma total lipids = plasma total cholesterol × 2.27 + plasma triglycerides +62.3 (Phillips et al., 1989). Plasma cotinine (ng/mL) was measured using liquid chromatography-tandem mass spectrometry. Chemical analysis was not done for 33 participants (1.4%) because of the absence of plasma sample. An additional 9 participants (0.3%) were excluded due to high background noise in chemical exposure data resulting from low sample volume, leaving 2292 participants to assess the associations between POPs and GDM risk.

2.4. Statistical analysis

We assessed the distribution of all chemicals and relevant covariates. Missing information on plasma cotinine, and total lipids (both < 1%) were imputed using multivariate imputation by chained equation (MICE) (White et al., 2011). Geometric means (GMs) and 95% confidence intervals (CIs) were calculated for each chemical after lipid adjustment (except for PFAS) in the overall cohort and among participants who developed GDM.

2.4.1. Individual chemical analysis

Individual chemicals were analyzed one at a time in relation to GDM risk. We used the wet-weight level of chemicals in statistical models but adjusted for plasma total lipids as a continuous variable (except for PFAS) to minimize potential biases associated with automatic lipid adjustment (Schisterman et al., 2005). However, POPs themselves can disturb lipid metabolism (Lee et al., 2007b), and adjustment for serum lipids can result in blockage of the causal pathway and over adjustment (Hernan et al., 2002). Hence, we conducted a sensitivity analysis without adjusting for serum lipids yet presented lipid-adjusted results to be more conservative. We excluded 16 chemicals with concentrations below the LOQ among > 95% of the study participants from analysis. For each chemical class, we also calculated total OCPs, total PBDEs, total PCBs, and total PFAS as the sum of detectable concentrations of all chemicals within that class. We also calculated total non-dioxin like PCBs as the sum of detectable concentrations of PCBs 138, 153, 170, and 180. In the end, 60 individual POPs (10 OCPs, 6 PBDEs, 35 PCBs, and 9 PFAS) and five summary measures of POPs were included in the analysis. For chemicals with concentrations below the LOQ among > 50% of the participants, we conducted a secondary analysis by dichotomizing exposure as detectable (> LOQ) versus non-detectable (< LOQ) levels using similar statistical models.

We used multivariate Poisson regressions with robust variance to estimate risk ratios (RRs) of GDM for each standard deviation (SD) increment in chemical concentration (Zou, 2004). Models were adjusted for maternal age (continuous), ppBMI (normal, overweight), education (less than college, some college/undergraduate, graduate/post-graduate), parity (nulliparous, multiparous), race/ethnicity (White, African American, Hispanic, Asian), family history of T2D among first-degree relatives (yes, no, not known), serum cotinine (ng/mL, continuous) and serum total lipids (ng/mL, continuous). Models for PFAS were not adjusted for serum total lipids, as this group of chemical is not considered lipophilic. Covariates included in the models were selected based on a priori evidence and causal diagram using a directed acyclic graph (DAG) (Sauer et al., 2013).

We investigated heterogeneity in the associations between POPs and GDM by women's ppBMI (normal, overweight) and family history of T2D (yes, no) by including interaction terms for these variables with individual POP in the statistical models as well as stratifying study participants by these variables. Suggestive evidence of interaction was observed for some chemicals and models at the level of $P < 0.05$, but none of the interaction terms remained significant after adjusting for multiple testing. Hence, we presented pooled analysis results without an interaction term, along with results stratified by mother's ppBMI and family history of T2D. We rescaled chemical concentrations by their SD in the overall cohort to aid in interpretation and comparison of point estimates across the stratifying groups. We used the false discovery rate (FDR) to adjust for multiple testing. Statistical significance was set at FDR < 0.05.

2.4.2. Chemical mixture analysis

Because POPs share structural and biological homology within and across chemical classes, interpretation of the effect of an individual POP as due solely to that compound can be misleading (Lee et al., 2014). We used weighted correlation network analysis (WGCNA; R package (Langfelder and Horvath, 2008)) to identify networks of interactive chemicals. This method has been used in genomics (Stuart et al., 2003), metabolomics, (Pei et al., 2017), and microbiome (Tong et al., 2013) research. The WGCNA method first obtains network adjacency matrix measured by Pearson correlation coefficients between chemicals and transforms it to topological overlap measures. Chemical networks were then defined as branches of a hierarchical clustering tree based on the topological overlap measure. The networks were detected after applying the dynamic tree cut method (Langfelder et al., 2008). These chemical networks were interpreted as mixtures of chemicals sharing similar exposure profiles or structural and biological characteristics. To summarize the chemical networks, we calculated the eigenvectors, which provided a mathematically optimal way of summarizing the co-occurrence patterns of all chemicals belonging to each network. To examine the associations of chemical networks with GDM risk, we used similar Poisson regression models with robust variance, adjusting for the same set of covariates to estimate risk ratios of GDM for each unit increment in the first eigenvector of respective chemical network. Analyses were conducted in the overall cohort as well as stratified by family history of diabetes and ppBMI.

All analyses were conducted in R, version 3.4.2 (Austria, Vienna).

3. Results

The distribution of sociodemographic and lifestyle characteristics of the study participants is presented in Table 1. The average age of women was 28.2 ± 5.5 years. Nearly 20% of the women reported having at least one first degree relative with T2D. All participants were reported to be non-smokers, as women with a history of smoking in the last 6 months before pregnancy were ineligible for the study. However, plasma cotinine concentration showed a wide variation (median [25th - 75th percentile] = 0.01 [0–0.04] ng/mL). Nine participants revealed concentrations above 100 ng/mL, suggesting possible secondhand smoke exposure. A total of 74 participants (3.2%) were diagnosed with GDM despite their low-risk antenatal profiles.

3.1. Associations of individual POPs with GDM risk

We identified several POPs significantly associated with GDM risk, although the associations were modified by family history of T2D and ppBMI (Table 2, Fig. S1). For example, eight PCB congeners (PCBs 170, 172_192, 177, 180, 183, 194, 196_203, 199), all heavily chlorinated with > 6 chlorine atoms, along with total PCBs and non-dioxin like PCBs showed significant positive associations with GDM (RRs range: 1.08–1.13 per 1-SD increment in plasma concentration) in the overall cohort. In stratified analysis by family history of T2D, 16 PCB congeners (PCBs 138_158, 146_161, 153, 156, 167, 170, 172_192, 177, 180, 182_187, 183, 194, 196_203, 199, 202, 206), all heavily chlorinated with ≥6 chlorine atoms, along with total PCBs and non-dioxin like PCBs showed significant positive associations with GDM among women with a family history of T2D (RRs range: 1.08–1.59 per 1-SD increment in plasma concentration), but not among women without a family history of T2D (*P*-for-interaction < 0.05 for PCB 146_161, 202, and 206). Eleven of these congeners (PCBs 153, 170, 172_192, 177, 180, 183, 194, 196_203, 199, 202, 206) along with total PCBs and non-dioxin like PCBs also showed significant positive associations with GDM among women with a ppBMI within the normal range (RRs range: 1.08–1.42 per 1-SD increment in plasma concentration). PCBs 138_158, 153, 170, 180, 182_187 were also among the most frequently detected PCBs in the study cohort; over 94%, 93%, 72%, 94%, and 64% of the study participants, respectively showed concentrations above the LOQ (Table S1).

Furthermore, four PFAS congeners (PFHpA, PFDoDA, PFNA, and PFOA) showed significant positive associations with GDM among women with a family history of T2D (RRs range: 1.22–3.18 per SD increment in plasma concentration), but not among women without a family history of T2D (*P*-for-interaction < 0.05 for PFDoDA, PFNA, and PFOA). PFHpA also showed a significant positive association with GDM among women with a ppBMI within the normal range. In general, most PFAS congeners were frequently detected in the study cohort. For PFOA and PFNA, nearly 100% of the study participants showed concentrations above the LOQ (Table S1).

In contrast, significant positive associations with GDM among women without a family history of T2D were observed for BDE 47 (RR = 1.18; 95% CI: 1.08–1.29 per 1-SD increment) and BDE 154 (RR = 1.23; 95% CI: 1.12–1.34 per 1-SD increment). The mean concentrations of these chemicals were also slightly higher among GDM cases than controls (Table S1). BDE 47 was also the most frequently detected PBDEs in the study cohort; over 92% of the participants showed concentrations above the LOQ.

OCPs were not associated with GDM in the overall cohort or in stratified analysis by family history of T2D. However, among women with a ppBMI within the normal range, HCB was significantly and inversely associated with GDM (RR, 95% CI: 0.88 (0.80–0.97). HCB was also among the most frequently detected OCPs in the study cohort; over 90% of the study participants showed concentrations above the LOQ (Table S1).

In secondary analysis of chemicals having concentrations below the LOQ in > 50% of the study participants, we observed largely consistent association pattern for concentrations above the LOQ compared to concentrations below the LOQ (Table S2).

3.2. Associations of chemical mixtures with GDM

As expected, exposure to POPs among the study participants was highly correlated (Fig. S2). We constructed four distinct chemical networks based on correlations among these chemicals (Fig. 1A). Network#1 (Turquoise) consisted of 17 chemicals, primarily PCBs with ≥6 chlorine atoms; network#2 (Brown) consisted of five chemicals, all PCBs with five chlorine atoms; network#3 (Blue) consisted of 13 chemicals, primarily PCBs with < 4 chlorine atoms; and network #4 (Gray) consisted of 25 compounds, primarily OCPs, PBDEs, and PFAS. Consistent with individual chemical analysis, the first eigenvector of network #1 revealed significant positive association with GDM in the overall cohort (RR = 1.11; 95% CI: 1.05, 1.18) and among women with a family history of T2D (RR = 1.18; 95% CI: 1.08, 1.28) and a ppBMI within the normal range (RR = 1.12; 95% CI: 1.05, 1.19) (Fig. 1B). Network#1 also revealed significant positive correlations with maternal age, education, non-White race/ethnicity, and plasma total lipids, whereas significant negative correlation with maternal ppBMI and no correlation with family history of T2D and plasma cotinine level (results not shown).

4. Discussion

In this multicenter, multiethnic prospective cohort study of 2292 non-obese pregnant women without a major pre-existing medical condition, we demonstrated that early pregnancy plasma concentration of several POPs were significantly and positively associated with GDM. Specifically, heavily chlorinated PCBs, along with the summary measure of total PCBs and non-dioxin like PCBs and some PFAS (i.e. PFOA, PFNA, PFHpA, PFDoDA) and PBDEs (i.e. BDE 47, BDE 154) showed signnificant positive associations with GDM, whereas HCB showed significant inverse association, although findings varied by characteristics such as women's family history of T2D and body adiposity status.

Table 1
Distribution of selected characteristics in the NICHD Fetal Growth Study, Singletons cohort.

Characteristics	All (n = 2292)
Age (y)	28.2 ± 5.5
Race/ethnicity, n (%)	
White/non-Hispanic	608 (26.5)
Black/non-Hispanic	601 (26.2)
Hispanic	639 (27.9)
Asian	444 (19.4)
Education, n (%)	
< College degree	640 (27.9)
Some college/undergraduate	1233 (53.8)
Graduate/post-graduate	419 (18.3)
Enrollment BMI (kg/m^2)	
19– < 25	1540 (67.2)
≥25– < 30	752 (32.8)
Parity, n (%) nulliparous	1129 (49.3)
Family history of diabetes, n (%)	
Yes	444 (19.5)
No	1787 (78.0)
Not known	59 (2.5)
Serum cotinine, ng/mL	1.24 (14.4)
Serum total lipids, mg/dL	608.8 (99.2)

Values are mean ± standard deviation, except where indicated otherwise.
Serum total lipids = (serum total cholesterol × 2.27) + serum triglycerides +62.3.

Table 2
Adjusted risk ratios of gestational diabetes (GDM) for each SD increment in plasma concentration of POPs in the overall cohort and stratified by women's family history of T2D and pre-pregnancy BMI.

POPs	> LOQ %	Overall cohort (n = 2292)		With family history of T2D (n = 447)		Without family history of T2D (n = 1792)		Normal pre-pregnancy BMI (n = 1525)		Overweight pre-pregnancy BMI (n = 745)	
		RR (95% CI)	FDR	RR (95% CI)	FDR	RR (95% CI)	FDR	RR (95% CI)	FDR	RR (95% CI)	FDR
PCBs [plasma (ng/g lipid)]											
Di-CB											
PCB5_8	16.3	1.23 (0.80,1.91)	7.7E-01	1.19 (0.61, 2.33)	6.9E-01	1.19 (0.68, 2.07)	9.9E-01	1.22 (0.63,2.35)	8.7E-01	1.28 (0.69,2.37)	9.8E-01
Tri-CB											
PCB18_17	23.7	1.15 (0.81,1.63)	7.7E-01	1.24 (0.59, 2.64)	6.7E-01	1.06 (0.70, 1.62)	9.9E-01	1.18 (0.51,2.75)	8.7E-01	1.15 (0.83,1.59)	9.8E-01
PCB31_28	40.6	1.12 (0.96,1.30)	4.2E-01	1.63 (0.76, 3.53)	4.3E-01	1.06 (0.89, 1.27)	9.9E-01	1.06 (0.86,1.33)	8.7E-01	1.28 (0.85,1.91)	9.8E-01
Tetra-CB											
PCB41_64	9.3	1.09 (0.86,1.36)	7.7E-01	1.39 (0.71, 2.71)	5.4E-01	1.01 (0.75, 1.36)	9.9E-01	1.06 (0.71,1.58)	8.9E-01	1.12 (0.90,1.40)	9.8E-01
PCB44	9.2	1.07 (0.88,1.30)	7.8E-01	1.18 (0.76, 1.84)	6.2E-01	1.03 (0.77, 1.39)	9.9E-01	1.08 (0.74,1.58)	8.7E-01	1.08 (0.88,1.32)	9.8E-01
PCB47_48_75	54.0	1.11 (0.89,1.38)	7.7E-01	1.39 (0.72, 2.66)	5.4E-01	1.00 (0.76, 1.32)	9.9E-01	1.11 (0.71,1.75)	8.7E-01	1.11 (0.90,1.37)	9.8E-01
PCB49_43	6.8	1.09 (0.87,1.38)	7.7E-01	1.17 (0.75, 1.85)	6.3E-01	1.06 (0.74, 1.52)	9.9E-01	1.12 (0.69,1.82)	8.7E-01	1.09 (0.87,1.36)	9.8E-01
PCB52_73	22.4	1.13 (0.87,1.46)	7.7E-01	1.20 (0.72, 1.97)	6.3E-01	1.13 (0.74, 1.71)	9.9E-01	1.28 (0.72,2.29)	7.7E-01	1.07 (0.86,1.32)	9.8E-01
PCB66_80	15.8	1.04 (0.91,1.19)	8.0E-01	1.31 (0.81, 2.12)	5.2E-01	0.99 (0.81, 1.22)	9.9E-01	1.02 (0.82,1.27)	9.3E-01	1.07 (0.89,1.29)	9.8E-01
PCB70_76	12.6	1.04 (0.87,1.23)	8.5E-01	1.16 (0.74, 1.08)	6.5E-01	0.99 (0.79, 1.25)	9.9E-01	1.00 (0.77,1.30)	9.7E-01	1.08 (0.87,1.34)	9.8E-01
PCB74_61	62.0	1.02 (0.90,1.16)	8.5E-01	1.25 (0.89, 1.77)	4.2E-01	1.01 (0.80, 1.28)	9.9E-01	1.06 (0.88,1.28)	8.5E-01	0.99 (0.84,1.16)	9.8E-01
Penta-CB											
PCB90_101_89	19.9	1.08 (0.87,1.34)	7.7E-01	1.30 (0.72, 2.35)	5.9E-01	1.03 (0.75, 1.41)	9.9E-01	1.07 (0.73,1.57)	8.7E-01	1.11 (0.87,1.42)	9.8E-01
PCB93_95	18.5	1.09 (0.88,1.36)	7.7E-01	1.19 (0.75, 1.89)	6.2E-01	1.08 (0.75, 1.54)	9.9E-01	1.11 (0.75,1.63)	8.7E-01	1.10 (0.86,1.41)	9.8E-01
PCB99	59.0	1.06 (0.91,1.23)	7.7E-01	1.35 (0.96, 1.89)	1.9E-01	1.02 (0.79, 1.31)	9.9E-01	1.08 (0.93,1.27)	6.4E-01	0.99 (0.76,1.29)	9.8E-01
PCB110	9.5	1.11 (0.89,1.38)	7.7E-01	1.41 (0.67, 2.99)	5.7E-01	1.07 (0.75, 1.52)	9.9E-01	1.07 (0.75,1.52)	8.7E-01	1.16 (0.89,1.52)	9.8E-01
PCB118_106	79.0	1.04 (0.88,1.23)	8.5E-01	1.27 (0.95, 1.72)	2.3E-01	0.98 (0.71, 1.36)	9.9E-01	1.06 (0.88,1.29)	8.5E-01	0.99 (0.77,1.26)	9.8E-01
PCB105_127	35.5	1.08 (0.93,1.27)	7.7E-01	1.31 (1.05, 1.64)	5.5E-02	1.02 (0.75, 1.40)	9.9E-01	1.14 (0.98,1.33)	3.1E-01	0.96 (0.78,1.18)	9.8E-01
Hexa-CB											
PCB137	7.0	1.06 (0.90,1.24)	7.9E-01	1.30 (1.04, 1.64)	6.4E-02	0.92 (0.67, 1.27)	9.9E-01	1.09 (0.95,1.26)	5.1E-01	0.95 (0.62,1.45)	9.8E-01
PCB138_158	94.1	1.11 (1.00,1.24)	1.9E-01	1.26 (1.12, 1.42)	**1.8E-03**	0.99 (0.72, 1.34)	9.9E-01	1.12 (1.01,1.24)	1.1E-01	0.98 (0.67,1.42)	9.8E-01
PCB146_161	37.7	1.04 (0.95,1.15)	7.7E-01	1.48 (1.20, 1.84)*	**1.8E-03**	0.94 (0.72, 1.23)*	9.9E-01	1.05 (0.96,1.15)	6.4E-01	0.97 (0.72,1.30)	9.8E-01
PCB153	93.8	1.12 (1.03,1.23)	5.6E-02	1.19 (1.08, 1.31)	**1.8E-03**	1.01 (0.77, 1.32)	9.9E-01	1.12 (1.04,1.22)	**2.4E-02**	0.97 (0.67,1.41)	9.8E-01
PCB156	34.0	1.14 (0.99,1.31)	2.4E-01	1.25 (1.10, 1.42)	**2.6E-03**	0.97 (0.64, 1.46)	9.9E-01	1.16 (1.03,1.30)	6.1E-02	0.95 (0.60,1.50)	9.8E-01
Hepta-CB											
PCB167	5.0	1.09 (0.97,1.22)	4.2E-01	1.34 (1.14, 1.57)	**1.8E-03**	1.00 (0.78, 1.29)	9.9E-01	1.10 (0.99,1.23)	2.7E-01	0.96 (0.68,1.36)	9.8E-01
PCB170	72.9	1.09 (1.06,1.11)	**5.0E-10**	1.08 (1.03, 1.13)	**2.3E-03**	1.04 (0.82, 1.32)	9.9E-01	1.08 (1.04,1.11)	**3.7E-05**	0.97 (0.54,1.77)	9.8E-01
PCB172_192	5.1	1.11 (1.06,1.17)	**7.0E-04**	1.14 (1.06, 1.22)	**1.8E-03**	0.94 (0.68, 1.30)	9.9E-01	1.11 (1.05,1.17)	**6.2E-04**	0.95 (0.59,1.52)	9.8E-01
PCB177	9.5	1.10 (1.04,1.18)	**1.4E-02**	1.15 (1.07, 1.24)	**1.8E-03**	1.00 (0.84, 1.20)	9.9E-01	1.10 (1.03,1.16)	**1.8E-02**	1.13 (0.81,1.58)	9.8E-01
PCB180	94.7	1.09 (1.06,1.11)	**2.4E-10**	1.08 (1.03, 1.13)	**2.1E-03**	1.08 (0.83, 1.39)	9.9E-01	1.08 (1.05,1.11)	**3.5E-05**	0.98 (0.58,1.66)	9.8E-01
PCB182_187	64.6	1.08 (1.01,1.16)	1.2E-01	1.17 (1.08, 1.27)	**1.8E-03**	0.98 (0.81, 1.19)	9.9E-01	1.08 (1.01,1.15)	1.1E-01	1.01 (0.66,1.54)	9.8E-01
PCB183	25.9	1.10 (1.06,1.14)	**1.1E-05**	1.11 (1.05, 1.17)	**1.8E-03**	0.96 (0.68, 1.36)	9.9E-01	1.09 (1.04,1.14)	**6.2E-04**	1.11 (0.79,1.55)	9.8E-01
Octa-CB											
PCB194	37.8	1.09 (1.06,1.12)	**3.1E-09**	1.08 (1.04, 1.13)	**2.1E-03**	1.03 (0.79, 1.35)	9.9E-01	1.08 (1.05,1.12)	**3.5E-05**	0.91 (0.54,1.55)	9.8E-01
PCB196_203	43.9	1.11 (1.07,1.15)	**1.5E-07**	1.11 (1.05, 1.17)	**1.8E-03**	1.09 (0.97, 1.22)	9.9E-01	1.10 (1.06,1.15)	**3.7E-05**	1.08 (0.85,1.38)	9.8E-01
PCB199	38.3	1.13 (1.07,1.19)	**5.0E-05**	1.14 (1.06, 1.22)	**1.8E-03**	1.10 (0.98, 1.23)	9.9E-01	1.12 (1.07,1.18)	**1.8E-04**	1.07 (0.83,1.37)	9.8E-01
PCB202	5.8	1.12 (1.03,1.22)	5.6E-02	1.31 (1.15, 1.49)*	**1.2E-03**	1.07 (0.96, 1.20)*	9.9E-01	1.12 (1.03,1.22)	**4.1E-02**	1.03 (0.74,1.44)	9.8E-01
Nona-CB											
PCB206	17.0	1.09 (1.02,1.16)	5.6E-02	1.38 (1.17, 1.62)*	**1.7E-03**	1.07 (0.99, 1.15)*	9.9E-01	1.10 (1.03,1.18)	**2.5E-02**	0.98 (0.75,1.28)	9.8E-01
Deca-CB											
PCB209	8.2	1.04 (0.96,1.11)	7.7E-01	1.66 (1.04, 2.66)	9.1E-02	1.01 (0.91, 1.13)	9.9E-01	1.03 (0.95,1.12)	8.3E-01	1.12 (0.79,1.58)	9.8E-01
Total PCB	100.0	1.11 (1.03,1.19)	**4.7E-02**	1.15 (1.06, 1.24)	**1.7E-03**	0.99 (0.73, 1.35)	9.9E-01	1.11 (1.04,1.18)	**7.5E-03**	0.87 (0.56,1.37)	9.8E-01
Non-dioxin like PCBs	100.0	1.12 (1.04, 1.19)	**1.4E-02**	1.15 (1.06, 1.24)	**1.7E-03**	0.99 (0.71, 1.38)	9.9E-01	1.11 (1.05, 1.18)	**3.6E-03**	0.92 (0.60, 1.42)	9.8E-01
PFAS [plasma (ng/mL)]											
NMeFOSAA	80.1	1.01 (0.85,1.19)	9.3E-01	0.96 (0.58, 1.6)	9.1E-01	1.02 (0.87, 1.21)	9.8E-01	1.08 (0.86,1.36)	8.2E-01	0.91 (0.61,1.36)	8.6E-01
PFDA	98.9	1.02 (0.86,1.20)	9.0E-01	1.10 (0.97, 1.25)*	2.9E-01	0.72 (0.39, 1.32)*	9.8E-01	1.02 (0.84,1.23)	9.4E-01	1.05 (0.74,1.48)	9.5E-01

(*continued on next page*)

Table 2 (*continued*)

POPs	> LOQ %	Overall cohort (n = 2292)		With family history of T2D (n = 447)		Without family history of T2D (n = 1792)		Normal pre-pregnancy BMI (n = 1525)		Overweight pre-pregnancy BMI (n = 745)	
		RR (95% CI)	FDR	RR (95% CI)	FDR	RR (95% CI)	FDR	RR (95% CI)	FDR	RR (95% CI)	FDR
PFDoDA	51.1	0.87 (0.42,1.80)	8.5E-01	3.18 (1.35, 7.52)*	**2.4E-02**	0.37 (0.12, 1.10)*	7.8E-01	0.95 (0.67,1.34)	9.1E-01	0.98 (0.37,2.59)	9.8E-01
PFHpA	42.0	1.18 (1.04,1.34)	5.6E-02	1.22 (1.12, 1.34)	**4.9E-04**	0.99 (0.75, 1.31)	9.9E-01	1.22 (1.11,1.33)	**2.0E-04**	1.06 (0.82,1.36)	8.6E-01
PFHxS	100.0	0.95 (0.73,1.23)	8.5E-01	1.03 (0.92, 1.16)	6.6E-01	0.87 (0.52, 1.46)	9.8E-01	1.01 (0.87,1.19)	9.4E-01	0.77 (0.44,1.36)	8.1E-01
PFNA	100.0	1.05 (0.82,1.35)	8.5E-01	1.43 (1.22, 1.68)*	**4.9E-04**	0.80 (0.50, 1.27)*	9.8E-01	1.11 (0.84,1.46)	8.2E-01	1.01 (0.79,1.31)	9.6E-01
PFOA	100.0	1.07 (0.86,1.34)	8.0E-01	1.27 (1.11, 1.45)*	**1.7E-03**	0.70 (0.43, 1.14)*	8.8E-01	1.10 (0.91,1.33)	6.6E-01	0.94 (0.71,1.25)	8.6E-01
PFOS	100.0	0.89 (0.69,1.16)	7.7E-01	1.03 (0.84, 1.27)	8.1E-01	0.86 (0.60, 1.23)	9.8E-01	0.77 (0.53,1.12)	4.4E-01	1.11 (0.75,1.64)	8.4E-01
PFUnDA	98.3	0.88 (0.67,1.17)	7.7E-01	1.29 (0.99, 1.69)*	1.4E-01	0.66 (0.37, 1.19)*	8.9E-01	0.91 (0.66,1.26)	8.7E-01	0.94 (0.62,1.43)	9.5E-01
Total PFAS	100.0	0.95 (0.73,1.25)	8.5E-01	1.16 (0.96, 1.40)	2.5E-01	0.78 (0.52, 1.16)	9.8E-01	0.95 (0.65,1.38)	9.1E-01	1.04 (0.71,1.52)	9.5E-01
PBDEs [plasma (ng/g lipid)]											
BDE28	37.2	1.02 (0.80,1.31)	9.1E-01	0.77 (0.28, 2.15)	6.9E-01	1.08 (0.94, 1.23)	9.9E-01	0.61 (0.16,2.35)	8.4E-01	1.48 (0.65,3.35)	9.8E-01
BDE47	92.8	1.13 (1.01,1.27)	1.4E-01	0.97 (0.65, 1.42)	9.2E-01	1.18 (1.08, 1.29)	**1.0E-02**	0.98 (0.77,1.24)	9.1E-01	1.18 (1.05,1.31)	2.3E-01
BDE99	61.6	0.97 (0.83,1.13)	8.5E-01	0.88 (0.70, 1.09)	4.6E-01	1.04 (0.92, 1.18)	9.9E-01	1.02 (0.95,1.09)	8.7E-01	0.85 (0.47,1.53)	9.8E-01
BDE100	71.6	0.82 (0.49,1.37)	7.7E-01	0.76 (0.44, 1.31)	5.4E-01	0.90 (0.49, 1.66)	9.9E-01	0.62 (0.33,1.18)	4.0E-01	0.92 (0.53,1.62)	9.8E-01
BDE153	42.4	0.64 (0.33,1.25)	5.4E-01	0.74 (0.34, 1.60)	6.2E-01	0.64 (0.26, 1.57)	9.9E-01	0.40 (0.13,1.25)	3.4E-01	0.87 (0.42,1.82)	9.8E-01
BDE154	38.6	1.16 (1.00,1.36)	1.9E-01	0.80 (0.51, 1.26)	5.4E-01	1.23 (1.12, 1.34)	**4.3E-04**	1.17 (0.96,1.43)	3.7E-01	1.16 (0.87,1.54)	9.8E-01
Total PBDEs	100.0	0.99 (0.79,1.24)	9.3E-01	0.62 (0.25, 1.57)	5.4E-01	1.03 (0.92, 1.15)	9.9E-01	0.62 (0.27,1.39)	5.4E-01	1.06 (0.87,1.30)	9.8E-01
OCPs [plasma (ng/g lipid)]											
GammaHCH	6.8	0.09 (0.00,35.68)	7.7E-01	0.02 (0, 494.13)	6.2E-01	0.10 (0, 224.75)	9.9E-01	0.54 (0.21,1.40)	4.9E-01	0.00 (0.00,1.16)	9.8E-01
HCB	90.1	0.90 (0.82,0.99)	1.2E-01	0.84 (0.72, 0.99)	9.1E-02	0.96 (0.89, 1.04)	9.9E-01	0.88 (0.80,0.97)	**4.1E-02**	0.99 (0.87,1.12)	9.8E-01
Oxychlordane	73.9	1.02 (0.85,1.23)	8.9E-01	0.83 (0.51, 1.34)	6.2E-01	1.12 (0.91, 1.38)	9.9E-01	0.84 (0.61,1.16)	6.4E-01	1.10 (0.86,1.40)	9.8E-01
TransChlordane	28.8	0.94 (0.83,1.06)	7.7E-01	1.01 (0.90, 1.13)	9.3E-01	0.92 (0.72, 1.17)	9.9E-01	1.02 (0.84,1.24)	8.9E-01	0.90 (0.79,1.03)	9.8E-01
TransNonachlor	90.3	1.00 (0.86,1.17)	9.7E-01	1.00 (0.72, 1.39)	9.9E-01	1.07 (0.93, 1.22)	9.9E-01	0.96 (0.77,1.19)	8.7E-01	1.03 (0.82,1.30)	9.8E-01
p,p'-DDE	99.9	1.01 (0.94,1.09)	8.5E-01	1.06 (0.89, 1.28)	6.4E-01	1.01 (0.93, 1.09)	9.9E-01	1.11 (0.98,1.26)	3.4E-01	0.98 (0.89,1.08)	9.8E-01
p,p'-DDD	28.2	0.99 (0.89,1.09)	8.6E-01	1.02 (0.91, 1.14)	8.1E-01	0.98 (0.89, 1.07)	9.9E-01	1.00 (0.87,1.13)	9.6E-01	0.98 (0.88,1.10)	9.8E-01
p,p'-DDT	65.1	0.95 (0.79,1.13)	8.0E-01	1.13 (0.89, 1.44)	5.4E-01	0.65 (0.23, 1.86)	9.9E-01	0.84 (0.38,1.83)	8.7E-01	0.96 (0.85,1.08)	9.8E-01
Mirex	32.3	0.95 (0.72,1.24)	8.5E-01	0.92 (0.64, 1.32)	7.3E-01	0.98 (0.78, 1.22)	9.9E-01	1.01 (0.84,1.21)	9.6E-01	0.73 (0.26,2.04)	9.8E-01
Total OCPs	100.0	1.01 (0.93,1.09)	8.9E-01	1.06 (0.84, 1.34)	6.9E-01	1.01 (0.92, 1.10)	9.9E-01	1.10 (0.96,1.28)	4.7E-01	0.97 (0.88,1.08)	9.8E-01

Abbreviations: SD = standard deviation; LOQ = level of quantification; T2D = type 2 diabetes; RR = risk ratio; FDR = false discovery rate.

Models were adjusted for maternal age (continuous), enrollment BMI (19–24.9; 25–29.9), education (< college; some college/undergraduate; graduate/post-graduate), parity (nulliparous; multiparous), race/ethnicity (white, African American, Hispanic, Asian), family history of type 2 diabetes among first degree relatives, serum cotinine level (continuous), and serum total lipids (continuous, mg/dL); for PFAS, models were not adjusted for serum total lipids. Serum total lipids = (serum total cholesterol × 2.27) + serum triglycerides + 62.3. In stratified analysis by family history of T2D, models were adjusted for the same set of covariates listed above except for the family history of type 2 diabetes. Similarly, in stratified analysis by women's pre-pregnancy BMI, models were adjusted for the same set of covariates listed above except for pre-pregnancy BMI.

Note: Separate models were run for each chemical. Significant (FDR < 0.05) *P*-values are in boldface. Estimates are rounded to two decimal points. In the overall cohort analysis, the models did not include an interaction term.

* $P < 0.05$ for chemical concentration and family history of type 2 diabetes interaction term. None of the interactions were significant after adjusting for multiple testing.

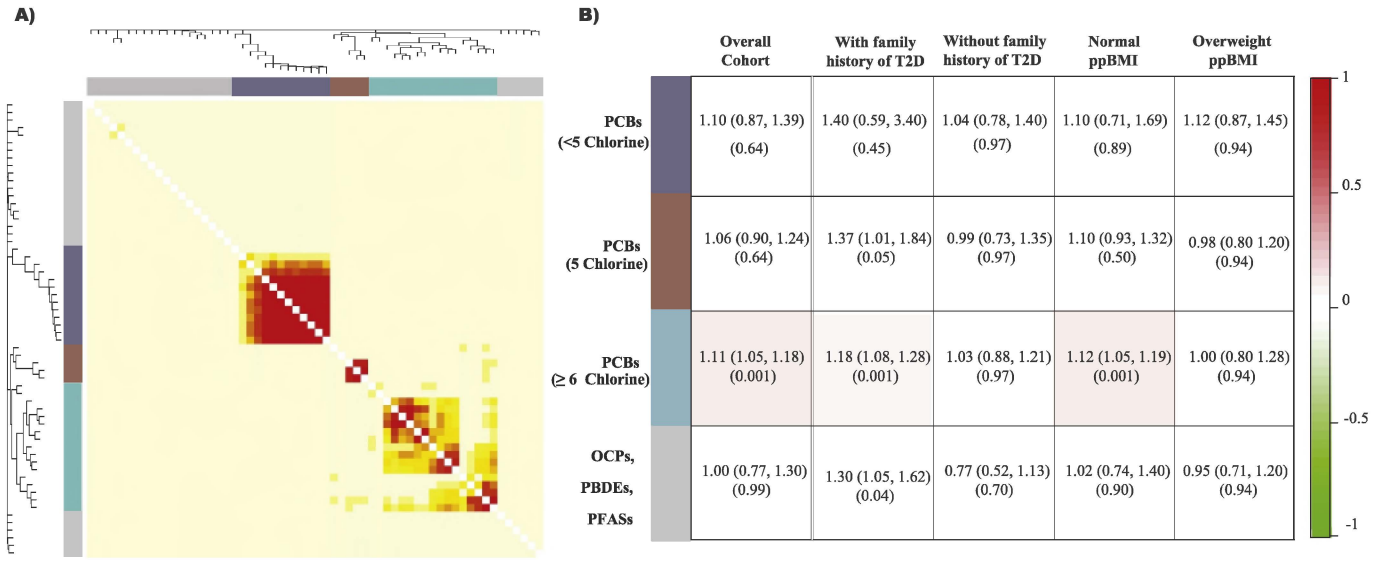

Fig. 1. Heat map and hierarchical clustering of POPs showing correlated chemical networks represented by four different colors (A). The associations between chemical networks and GDM risk in the overall cohort and stratified by family history of T2D and pre-pregnancy BMI are shown (B). Each cell reports RR (95% CI) along with FDR corrected *p*-values derived from the association of the first eigenvector of each chemical network with GDM using modified Poisson regression with robust variance adjusted for covariates. The table is color-coded by risk ratios according to the color legend. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Of particular note, these associations were observed among healthy pregnant women with low-risk antenatal profiles and at concentrations, the US general population were exposed to during the same period (Centers for Disease Control and Prevention, 2017).

Most robust association with GDM was observed for heavily chlorinated PCBs, where PCBs with six or more chlorine atoms showed significant positive associations. Consistently, the summary measures of total PCBs and non-dioxin like PCBs (138, 153, 170, 180) along with the chemical network comprised of six or more chlorine atoms showed significant positive associations with GDM. Previous studies have reported inconsistent findings for associations between PCBs and GDM. In Rhea pregnancy cohort in Greece (n = 939), the sum of first trimester serum concentrations of PCBs (118, 138, 153, 156, 170, and 180) and dioxin-like PCBs (118, 156), but not non-dioxin-like PCBs (153, 138, 170, 180) showed significant positive associations with GDM in a dose-dependent manner (Vafeiadi et al., 2017). A small case-control study (n = 140) restricted to primiparous women without a family history of T2D also reported positive associations for PCBs 118, 153, 187 and the summary measure of PCBs (28, 118, 138, 153, 180, 187) with GDM. However, first trimester urinary concentrations of PCBs 118, 138, 153, 180, and the summary measure of PCBs (118, 138, 153, 180) or non-dioxin-like PCBs (138, 153, 180) showed null associations in the Canadian MIREC birth cohort (n = 1274) (Shapiro et al., 2016). Interestingly, the US LIFE Study reported significant inverse associations for maternal pre-pregnancy serum concentrations of PCBs 138, 153, 156, 167, 170, 172, 178, 180, and 194 among participants planning to become pregnant (n = 258) (Jaacks et al., 2016). However, in the general population, PCBs were consistently associated with insulin resistance and T2D (Lee et al., 2014; Lee, 2012; Magliano et al., 2014). Similar findings were reported for the summary measures of total PCBs and non-dioxin like PCBs (Aminov et al., 2016).

Studies have also suggested heterogeneous associations for PCBs by the degree of chlorination, where heavily chlorinated PCBs were more likely to be associated with obesity, insulin resistance, lipid abnormalities, and T2D (Lee et al., 2011a; Lee et al., 2011b; Lee et al., 2010). It is believed that the degree of chlorination is an important determinant for the toxicity of chlorinated POPs, where POPs with a greater number of chlorine atoms persist longer in the environment and are more toxic (Lee et al., 2010). However, such pattern was not consistent across studies (Kim et al., 2014).

Our observed associations between PFAS and GDM are also in consistent with findings from the US LIFE study reporting higher odds of GDM associated with higher pre-conception serum concentrations of several PFAS congeners, although the associations were statistically significant only for PFOA (Zhang et al., 2015). In contrast, two other prospective studies reported null associations for several PFAS congeners (Shapiro et al., 2016; Valvi et al., 2017). In the general population, PFOA and PFOS have consistently shown significant positive associations with beta-cell function, HOMA-IR, fasting proinsulin, insulin, and glycated hemoglobin (Cardenas et al., 2017; Lin et al., 2009), providing evidence to support our observed findings in the pregnant population.

Our findings for OCPs are mostly consistent with other prospective studies that reported null associations with GDM (Vafeiadi et al., 2017; Shapiro et al., 2016; Smarr et al., 2016; Valvi et al., 2017) except for HCB, which showed significant inverse association among women with normal ppBMI in our cohort. Our findings for OCPs also contradict with the evidence in the general population, where OCPs have been consistently associated with insulin resistance and T2D (Lee et al., 2014; Lee, 2012; Magliano et al., 2014). The exact reason behind this inconsistency remains to be studied. Epidemiological associations for PBDEs with GDM is mixed. In US LIFE study, pre-conception serum concentration of BDE-47 was inversely associated with GDM, whereas BDE-153 was positively associated (Smarr et al., 2016). Another study reported higher odds of GDM with higher first-trimester serum concentrations of BDE-153, 154, and 183 (Liu et al., 2018).

While the precise molecular mechanism has yet to be elucidated, experimental studies and animal models support a diabetogenic effect of POPs through adipogenesis (Tang-Peronard et al., 2011; Janesick and Blumberg, 2016), insulin resistance and β-cell dysfunction (Cardenas

et al., 2017; Kim et al., 2014), and lipid abnormality (Lee, 2012; Heindel et al., 2017; Robledo et al., 2015). Exposure to POPs of various classes, including PCBs, PBDEs, and PFAS have been linked with activation of peroxisome proliferator-activated receptor-α (PPAR-α) (Shipley et al., 2004) (Pyper et al., 2010) and receptor-γ (Janesick and Blumberg, 2016; Kamstra et al., 2014), which are ligand-activated transcription factors involved in gene expression, lipid metabolism, glucose homeostasis, and inflammation. Also, studies have demonstrated that sub-chronic exposure to POP-mixture at low-doses similar to the background concentrations observed in human populations can induce mitochondrial dysfunction (Ruzzin et al., 2010), which can lead to insulin resistance and secretary dysfunction of pancreatic β-cells (Szendroedi et al., 2011). Mitochondrial dysfunction also plays a critical role in chronic inflammation (Lopez-Armada et al., 2013), where chronic low-grade inflammation in the adipose tissue can trigger metabolic dysfunctions, such as insulin resistance leading to T2D (Hotamisligil, 2006).

The heterogeneity of findings for POPs in relation to GDM across studies could be due to the differences in study population, study design, the timing of sample collection, and laboratory techniques used to quantify exposure. Inconsistent findings across studies could also be due to the distributional difference in POP mixture across populations, along with possible non-linear exposure-outcome relationship, leading to differing associations across the range of exposure (Lee et al., 2014). POPs are well known for their endocrine disrupting property (EDC). Studies have reported an inverted U-shaped dose-response relationship between chlorinated POPs and endocrine and mitochondrial dysfunctions, similar to that in case of hormones (Lee et al., 2014). For example, within the lower dose range, the risk of T2D substantially increased with minimal increase in exposure to chlorinated POPs, whereas the risk only slightly increased with increasing exposure within higher doses of POPs (Lee et al., 2011b; Lee et al., 2010). The concentrations of frequently detected POPs in our cohort were much lower than that reported in US pregnant population in NHANES 2003–2004 (Woodruff et al., 2011), but similar to that reported in the US general population during 2009–2013 (Centers for Disease Control and Prevention, 2017). Comparing with other prospective cohorts where GDM was studied, the concentrations of POPs in our cohort were lower than that reported in the Faroe Islands (Valvi et al., 2017) and Rhea pregnancy cohorts (Vafeiadi et al., 2017) in Grece, but comparable to that reported in the MIREC pregnancy cohort in Canada (Shapiro et al., 2016) and much lower than that reported in the US LIFE Study cohort (Jaacks et al., 2016; Smarr et al., 2016). Because exposure to POPs in our cohort was very low, it is possible that we might have captured the linear segment of the potential non-linear dose-response relationship within the lower dose range. In populations with higher exposure to POPs, an attenuated or even inverse association with GDM could be seen, as was probably the case in US LIFE Study cohort despite having similar reproductive age profiles of the study participants as our cohort (Jaacks et al., 2016).

Our findings also suggested possible effect modifications by women's ppBMI. The adipose tissue acts as an internal buffer by sequestering lipophilic chemicals into fat globules, which in turn may result in lower circulatory level of POPs (Bourez et al., 2012). Indeed, we observed lower plasma concentration of most POPs among women with a normal ppBMI compared to women with a ppBMI within the overweight range (data not shown). Consistently, we observed significant positive associations for heavily chlorinated PCBs among women with a ppBMI within the normal range. Furthermore, our results suggested that women's family history of T2D might also modify the effect of certain PFAS on GDM risk. PFAS also appeared to have an interactive effect with women's family history of T2D, where a higher risk of GDM was observed for women with a family history of T2D. Genetic susceptibility plays a vital role in modifying the risk of environmental chemicals on T2D (Franks, 2011), although evidence for GDM is sparse. Most previous studies on GDM did not account for women's family history of T2D. Future studies are warranted to investigate potential gene-environment interactions between PFAS exposure and T2D risk loci in relation to GDM.

Our study has several potential limitations, which need to be considered in weighing the findings. Concentrations of POPs measured in this cohort were very low, as evident by many measurements below the LOQ for a number chemicals, resulting in potential measurement error, which could bias our results towards the null (Richardson and Ciampi, 2003). For analysis, we used machine-read values for concentrations below the LOQ, a strategy to yield least biased estimates compared to simple imputation strategies (Schisterman et al., 2006). Moreover, we conducted a sensitivity analysis for chemicals having > 50% of the measurements below the LOQ by dichotomizing exposure as detectable versus non-detectable levels and observed similar association pattern. Furthermore, a total of 123 women underwent a 75 g 2-h OGTT test, instead of the 100 g 3-h OGTT test. A study comparing the two screening approaches reported lower sensitivity for the 2-h OGTT test compared to the 3-h test (Soonthornpun et al., 2003). Therefore, it is possible that we might have missed to identify a few GDM cases in our cohort. However, the average exposures to POPs were not significantly different between participants who underwent the 2-h test versus the 3-h test, suggesting that our estimates for GDM risk were likely not biased by variations in the OGTT test.

Notable strengths of this present study include the prospective design to capture incident GDM cases and a relatively large sample size of pregnant US women with a multiracial/ethnic background. We also have collected comprehensive questionnaire and biomarker data that allowed us to control for a variety of confounding variables as well as assessing potential effect modifications by ppBMI and family history of T2D. We also adjusted for maternal plasma total lipids in our analysis, as circulatory lipid levels can influence the plasma concentration of lipophilic chemicals, such as the chlorinated and brominated POPs. Thus, risks would have been overestimated had we not adjusted for plasma lipids (Magliano et al., 2014). However, lipids could also lie within the causal pathways between POPs and GDM, as POPs are known to be associated with dyslipidemia (Lee et al., 2011a), and elevated lipids are linked with GDM (Ryckman et al., 2015). Therefore, adjusting for plasma lipids could also result in over adjustment (Robins, 2001). However, we observed consistent findings with or without adjusting for plasma total lipids, although presented adjusted results to be more conservative.

We applied a novel statistical approach to assess the effect of a mixture of highly correlated POPs on GDM risk using weighted correlation network analysis approach (Langfelder and Horvath, 2008). POPs are generally highly correlated, and it is not always possible to determine the effect of an individual POP when participants are exposed to a mixture of POPs. Moreover, the impact of a single POP cannot be interpreted as due solely to that compound; instead, they likely reflect the properties of the POP mixture of which the compound is a part (Lee et al., 2006). Therefore, focusing on individual POPs can be misleading. A notable significance of this study is that unlike previous studies, we applied a novel mixture analysis approach in addition to the individual chemical analysis and found consistent results.

5. Conclusions

Findings from this prospective cohort of multiracial/ethnic pregnant women suggested that environmental exposure to heavily chlorinated PCBs and some PFAS and PBDEs were significantly and positively associated with GDM risk, although findings varied by characteristics

such as women's family history of T2D and body adiposity status. Of particular note, these associations were observed among pregnant women with low-risk antenatal profiles and at concentrations the US general population was exposed to during the same period.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.01.027.

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