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Profiles and Predictors of Environmental Chemical Mixture Exposure among Pregnant Women: The Health Outcomes and Measures of the Environment Study

Geetika Kalloo[†,*], **Gregory A. Wellenius**[†], **Lawrence McCandless**[‡], **Antonia M. Calafat**[§], **Andreas Sjodin**[§], **Margaret Karagas**[‖], **Aimin Chen**[⊥], **Kimberly Yolton**[#], **Bruce P. Lanphear**[‡,+], **Joseph M. Braun**[†]

[†]Department of Epidemiology, Brown University, Providence, Rhode Island 02912, United States

[‡]Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia V5A 1S6, Canada

[§]Centers for Disease Control and Prevention, Atlanta, Georgia 30333, United States

[‖]Department of Epidemiology, Dartmouth College, Hanover, New Hampshire 03755, United States

[⊥]Department of Environmental Health, University of Cincinnati, Cincinnati, Ohio 45267, United States

[#]Department of Pediatrics, Cincinnati Children's Hospital Medical Center, College of Medicine, University of Cincinnati, Cincinnati, Ohio 45229, United States

[+]Child and Family Research Institute, BC Children's and Women's Hospital, Vancouver, BC, Canada Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia V5Z 4H4, Canada

Abstract

Pregnant women are exposed to numerous environmental chemicals, but there is limited understanding of chemical mixture exposure profiles and predictors. In a prospective cohort of 389 pregnant women from Cincinnati, OH, we used biomarkers to estimate exposure to 41 phenols, phthalates, metals, organophosphate/pyrethroid/organochlorine pesticides,

[*]**Corresponding Author**: Geetika Kalloo. Tel: +1 (401) 863-5397; geetika_kalloo@brown.edu.

Author Contributions

G.K. analyzed and interpreted all participant data, and drafted the paper. All analysis was conducted under the guidance of J.M.B., who was also a major contributor in interpreting the data, developing, and writing the paper. G.A.W., L.M., M.R.K., A.S., A.M.C., A.C., K.Y., and B.P.L. provided critical revisions of the manuscript for important intellectual content. All authors read and approved the final paper.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.8b02946.

Table S1: Additional characteristics of urinary or serum chemical concentrations among pregnant women. Table S2: Geometric means of chemical concentrations per cluster. Table S3: Loading factors for the principal component analysis. Table S4: Unadjusted odds of cluster membership among pregnant women in the HOME Study (PDF)

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polychlorinated biphenyls, polybrominated diphenyl ethers, perfluoroalkyl substances, and environmental tobacco smoke. Using pairwise correlations, *k*-means clustering, and principal component analysis (PCA), we identified several profiles of chemical exposure. Chemicals within structurally, commercially, or industrially related chemical classes (e.g., phthalates) were moderate to strongly correlated compared to unrelated chemicals (e.g., pyrethroid pesticides and environmental tobacco smoke). Using *k*-means clustering and PCA, we identified 3 clusters of women (N = 106, 158, and 125) and 6 PC scores, respectively, that characterized profiles of cumulative chemical exposure. The first two PC scores significantly varied by cluster, indicating that some of these profiles could be identified using both methods. Cluster membership and PCA scores were associated with race, marital status, consumption of fresh fruits and vegetables, and parity. Future work could use clusters and PCA scores to characterize environmental chemical mixture exposures in other cohorts of pregnant women and predict potential health effects of environmental chemical mixture exposure.

INTRODUCTION

Exposure to some environmental chemicals, particularly during the sensitive gestational period, may be neurotoxic, immunotoxic, carcinogenic, and obesogenic to children.[1–5] The developing fetus may be more susceptible to environmental chemical exposures during this period of rapid growth and development because they cannot yet efficiently metabolize and excrete toxicants.[6–8] Biomonitoring studies indicate ubiquitous exposure to numerous chemicals among pregnant women in the United States.[9] Importantly, a number of chemicals found in maternal urine and blood readily cross the placenta and are routinely present in the fetus or amniotic fluid.[10–12]

Humans are simultaneously exposed to a mixture of chemicals from contaminated air, food, drinking water, dust, and consumer products.[9,13] Pesticides, perfluoroalkyl substances (PFAS), and phthalates are just a few classes of chemicals detected regularly in household dust, drinking water, air, food packaging, home furnishings, personal care, and consumer products.[14–19] To date, most research on gestational chemical exposures has focused primarily on the health effects of individual chemicals or classes of chemicals, leaving us with incomplete information on the potential cumulative or interactive effects of these exposures.[20] Moreover, there are little data about the profiles and determinants of chemical mixtures routinely found in pregnant women. Two prior studies among pregnant women in Canada and Spain found that structurally, commercially, or industrially related chemicals were more strongly correlated with each other than unrelated chemicals.[21,22] However, we are not aware of any studies examining the profiles and predictors of chemical mixtures among pregnant women in the United States.

Characterizing the profiles of gestational exposure to chemical mixtures can help us identify combinations of chemical exposures that may be related to children's health.[7,23] Therefore, we aimed to understand the relationships between 41 environmental chemical concentrations using two different dimension reduction techniques with the goal of developing new metrics to characterize exposure to mixtures of environmental chemicals in 389 pregnant women from Cincinnati, OH. Moreover, we identified determinants of these profiles in order

to better understand sociodemographic, behavioral, lifestyle, and perinatal predictors of exposure and provide more comprehensive information for effective interventions.

METHODS

Study Participants.

We used data from the Health Outcomes and Measures of the Environment (HOME) Study, a prospective pregnancy and birth cohort in the United States. Participant eligibility, recruitment, and follow-up have been described in detail elsewhere.[24] Briefly, we recruited pregnant women from Cincinnati, Ohio area prenatal clinics from March 2003 through January 2006. We enrolled women who were aged 18 years or older, 16 ± 3 weeks of gestation, living in a home-built before 1978, not on medications for thyroid disorders or seizures, planning to continue prenatal care and deliver at the collaborating clinics and hospitals, planning to live in the Cincinnati, OH area for the next year, fluent in English, and had no diagnosis of diabetes, bipolar disorder, schizophrenia, HIV infection, or cancer that resulted in radiation treatment or chemotherapy. Of the 1263 eligible women, 468 women enrolled in our study (37%), 67 dropped out before delivery, and there were 3 stillbirths and 9 sets of twins. The remaining 389 mother–child pairs delivered a live born singleton infant. For these analyses, we included all pregnant women who had at least one chemical concentration measured in urine or blood at either the 16 or 26 week clinic visit.

The institutional review boards (IRB) of Cincinnati Children's Hospital Medical Center (CCHMC) and the participating delivery hospitals approved this study protocol. The Centers for Disease Control and Prevention (CDC) and Brown University deferred to CCHMC IRB as the IRB of record. Women provided written informed consent after all the study protocols were explained to the participants.

Chemical Exposures.

We assessed exposure to >100 environmental chemicals during pregnancy using chemical concentrations measured in urine, serum, or blood.[24] The broad classes of chemicals included phenols, phthalates, metals, pesticides, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), PFAS, and cotinine. Mothers provided up to two urine samples at 16 and 26 weeks of gestation. At these visits, and within 48 h of delivery, we collected maternal blood samples via venipuncture and subsequently isolated serum from whole blood. All urine samples were stored at −20 °C, and blood and serum samples were stored at −80 °C, until they were shipped on dry ice to the CDC for analysis. For this analysis, we focused on 41 chemicals (or their metabolites) measured in HOME Study participants that are either known or suspected to increase the risk of adverse health outcomes in children (Table 1).

Using solid phase extraction coupled with high-performance liquid chromatography isotope dilution-tandem mass spectrometry, we measured the total (free plus conjugated) urinary concentrations of methyl-, propyl and butyl-parabens, bisphenol A (BPA), triclosan, mono-*n*-butyl-phthalate (MBP), monobenzyl phthalate (MBzP), mono(3-carboxypropyl) phthalate (MCPP), monoethyl phthalate (MEP), monoisobutyl phthalate (MiBP), four di-2-

ethylhexyl phthalate (DEHP) metabolites (mono-2-ethylhexyl phthalate [MEHP], mono-2-ethyl-5-hydroxyhexyl phthalate [MEHHP], mono-2-ethyl-5-oxohexyl phthalate [MEOHP], and mono-2-ethyl-5-carboxypentyl phthalate [MECPP]), and 3-phenoxybenzoic acid (a metabolite of pyrethroid insecticides).[25–27] We measured urinary concentrations of six dialkyl phosphates (metabolites of organophosphate insecticides) using gas chromatography isotope dilution-tandem mass spectrometry.[28]

Urinary arsenic (As) and cadmium (Cd) concentrations were measured by inductively coupled plasma-mass spectrometry.[29,30] In our analyses, we examined the summed concentrations of As III, dimethylarsinic acid (DMA), monomethylarsonic acid (MMA), and As V. To control for individual variation in urine dilution for the above listed nonpersistent chemicals and metals, chemical concentrations were standardized according to urinary creatinine concentrations (units of μg/g creatinine), measured with a kinetic Jaffe reaction.

Blood lead (Pb) and total mercury (Hg) were quantified using inductively coupled plasma mass spectrometry.[31,32] We measured serum concentrations of 32 PCBs, 9 organochlorine (OC) pesticides, and 9 PBDEs using previously described gas chromatography-tandem mass spectroscopy methods.[33,34] We lipid-standardized serum concentrations of OC pesticides, PCBs, and PBDEs, using serum measurements of triglycerides and total cholesterol determined via standard enzymatic methods.[35] Finally, we quantified serum concentrations of cotinine, a metabolite of nicotine and biomarker of tobacco smoke exposure, and of 10 PFAS using high-performance liquid chromatography-tandem mass spectroscopy.[36,37]

Because many individual chemical concentrations within a given class are highly correlated due to shared exposure sources (e.g., PCBs) or common metabolic pathways (e.g., metabolites of DEHP). Thus, we summed the concentrations of specific chemicals or used individual chemicals within a class as an indicator of exposure to parabens, DEHP, organophosphate pesticides, PCBs, and PBDEs. We calculated the molar sum of three parabens (∑parabens: methyl-, propyl, and butyl parabens), four metabolites of DEHP (∑DEHP), and six dialkyl phosphate metabolites (∑DAP: diethyldithiophosphate, diethylphosphate, diethylthiophosphate, dimethyldithio-phosphate, dimethylphosphate, and dimethylthiophosphate) of organophosphate pesticides. We also summed the concentrations of the four most commonly occurring PCBs ($\sum_4$PCBs: PCB-138/158, PCB-118, PCB-153, and PCB-180). To assess PBDE exposure, we used serum BDE-47 concentrations because it is the most abundant PBDE congener in our study and concentrations were available for most participants (94%). Additionally, BDE-47 was moderate to strongly correlated with other PBDEs (PBDE-28: $r = 0.9$, PBDE-85: $r = 0.9$, PBDE-99: $r = 0.9$, PBDE-100: $r = 0.9$, PBDE-153: $r = 0.5$, PBDE-154: $r = 0.8$).

Because chemical concentrations were not normally distributed, we $\log_{10}$-transformed all chemical concentrations to satisfy normality assumptions of our models. Log_{10}-transformed concentrations were averaged when a woman provided a sample at both the 16 and 26 week visits. All values below the limit of detection (LOD) were assigned a value of LOD/√2.[38]

Predictors of Chemical Exposure Mixtures.

HOME Study research staff administered standardized surveys to participants to ascertain maternal sociodemographic, behavioral, and lifestyle factors at the baseline study visit during the second trimester. Sociodemographic variables included maternal race, age, education, marital status, and household income. Behavioral and lifestyle factors included the frequency of fresh fruit, vegetable, and fish consumption during pregnancy. Research staff abstracted perinatal information, including participant's parity and body mass index (BMI), from medical records. Maternal BMI, age, and household income were treated as continuous variables, and the remaining variables were characterized as categorical variables.

Statistical Analysis.

In order to account for missing chemical concentrations in the data, we imputed missing values among women who had at least one measured chemical concentration during pregnancy using the Markov Chain Monte Carlo (MCMC) method.[39] The imputations were done using all available chemical concentrations as well as the sociodemographic, behavioral, lifestyle, and perinatal variables listed above. We generated 20 imputed data sets, averaged the imputed values, and used these values for all further analysis.

We conducted three sets of statistical analyses to understand the profiles of exposure to chemical mixtures among pregnant women. We began with simpler methods to understand the relationship between individual chemicals before moving onto more complex dimension reduction techniques. To account for varying scales of individual chemicals, we converted the $\log_{10}$-transformed chemical concentrations to z-scores when using more complex techniques.

We first calculated pairwise Pearson's correlation coefficients between individual chemical concentrations to understand the bivariate relations among chemical concentrations. We also examined the central tendency and range of correlation coefficients overall, within, and between families of chemicals.

Next, we used *k*-means clustering to classify pregnant women into *k* clusters based on their chemical concentrations.[40] The *k*-means algorithm uses Euclidian geometry to compute a cluster centroid and assign observations to a cluster such that the summed distances between the observations and cluster centroids are minimized. The number of clusters is assigned *a priori* based on subject matter knowledge. Because we did not have prior knowledge of the number of unique clusters in our data set, we explored solutions with 2, 3, and 4 clusters to ensure that there were a reasonable number of women within each cluster for interpretability. Among the 2, 3, and 4 cluster solutions, we selected the optimal number of clusters using the cubic cluster criterion (CCC), a test statistic where lower values indicate more distinct clustering of the data.[41] The 3-cluster solution had the lowest CCC value. We also calculated the geometric mean (GM) chemical concentrations among women within each cluster.

Third, we performed a principal components analysis. We began by conducting an exploratory PCA with no constraints on the total number of principal components. We then restricted our PCA to 6 principal components by examining Scree plots and selecting

a number of principal components that explained ≥50% of the variance in our data. We compared our PCA results to the *k*-means clustering results by calculating the mean PC scores for each cluster and using linear regression to test whether PC scores varied by cluster.

Finally, we used multinomial logistic regression and multivariable linear regression to identify predictors of cluster membership and principal component (PC) scores for each of the six PCs, respectively. PC scores were calculated by multiplying the original chemical concentration z-scores by that chemical's PCA loading value for each principal component. We included maternal race, age, education, marital status, income, BMI, parity, fresh fruit, vegetable, and fish consumption as predictors in all of these models.

We used SAS version 9.4 (SAS Institute, Inc. Cary, NC) and R version 3.2.3 (R Core Team, Vienna, Austria) for all statistical analysis.

RESULTS

Among 389 women who delivered a live singleton newborn in the HOME Study, all had complete data for phenols, phthalates, and Pb (Table 1, Table S1). A total of 231 women had complete data for all chemical concentrations with the largest number of women missing data for oxychlordane ($N = 87$) and hexachlorobenzene ($N = 79$).

Overall, we observed that chemical concentrations within a chemical class were more correlated with each other than with chemical concentrations from another class (Figure 1). The mean Pearson pairwise correlation (r) for all chemical concentrations was 0.08 (Median: 0.08, Range: −0.44, 0.90). Among all chemical concentrations, 23 (6%) pairwise correlations were $r > 0.40$; these pairs tended to be of the same chemical class (87%). For example, correlations among the organochlorine pesticides ranged from 0.36 to 0.90, with the strongest correlation between oxychlordane and transnonachlor ($r = 0.90$). Correlations among PFAS ranged from 0.37 to 0.64; the strongest correlation was observed between perfluorooctanesulfonate (PFOS) and perfluorohexanesulfonate (PFHxS) ($r = 0.64$) (Figure 1). Additionally, there were some weaker positive correlations between chemical concentrations from different classes. Pb and cotinine ($r = 0.33$), Pb and BDE-47 ($r = 0.12$), ∑parabens and MEP ($r = 0.37$), and BDE-47 and cotinine ($r = 0.30$) were weakly to moderately correlated with each other. Generally, chemicals from different classes were not correlated (e.g., DEHP and Hg $r = -0.03$ and PCB and MBP $r = 0.02$). There were some moderate negative correlations of note, with the strongest between cotinine and benzophenone-3 ($r = -0.44$) and cotinine and triclosan ($r = -0.31$).

Using *k*-means clustering, we identified three distinct clusters of women's chemical concentrations (Figure 2, Table S2, Table S3). Women in cluster 1 ($N = 106$) had the highest GM of 20 chemical concentrations, while women in cluster 2 ($N = 158$) had the highest GM concentrations of 2 chemicals and intermediary concentrations of 23 chemicals. Women in cluster 3 ($N = 125$) had the highest GM concentrations of 6 chemicals and lowest GM concentrations of 17 chemicals. Women in cluster 1 had profiles of chemical concentrations consistent with higher exposure to most phenols, three phthalates, several

metals, organophosphate and organochlorine pesticides, PCBs, and several PFAS. The profile of chemical concentrations among women in cluster 2 was indicative of higher exposure to two phthalates and intermediate exposure to phenols, metals, organophosphate and organochlorine pesticides, PCBs, several PFAS, and tobacco smoke. Women in cluster 3 had profiles of chemical concentrations consistent with higher exposure to parabens, one phthalate (monoethyl phthalate), lead, BDE-47, one PFAS, and tobacco smoke exposure, and intermediate exposure to several phthalates and one PFAS.

Using PCA, we found that 6, 13, and 21 principal components explained at least 50, 80, and 95% of the variance in chemical concentrations, respectively. Each additional component beyond six explained less than 5% of the total variance in the data. We constrained the PCA to six principal components to explain the majority of the variation in the data and reduce the dimensionality of the data. Then, we compared the variance that each PC explained in each chemical concentration and characterized each PC by the chemicals that had the highest amount of variance accounted for by that PC (Figure 3, Table S4).

PC1 explained most of the variance in oxychlordane, *trans*-nonachlor, benzophenone-3, triclosan, As, ∑DAPs, and $\sum_4$PCBs (Table S5). Thus, we characterized PC1 as being indicative of exposure to organochlorine compounds, phenols, and As. In addition, PC1 explained at least some of the variance in the majority of chemical concentrations. PC2 explained most of the variance in MBP, MBzP, MCPP, MiBP, DEHP, PFOS, PFNA, PFOA, PFHxS, and 3-phenoxybenzoic acid and we characterized this component as being indicative of phthalate, PFAS, and pyrethroid pesticide exposure. We characterized PC3 as an indicator of exposure to lead, OC pesticides, HCB, and environmental tobacco smoke. PC4 did not explain the highest variance for any of the chemicals, but all phthalates had loading factors greater than 0.20 and PC4 explained some variance in most chemical concentrations. PC5 explained most of the variance of the parabens, MEP, and Hg. Finally, PC6 explained the highest variance for BPA, Cd, and PBDE-47.

In some cases, we observed higher mean PC scores among women in clusters where the specific PC score explained variation in chemical concentrations that were also higher in concentration in that cluster (Table 2). Specifically, women in cluster 1 had higher mean PC scores for three of the six principal components than women in clusters 2 or 3, which was consistent with their pattern of having the highest GM concentrations of most chemicals. In addition, 4 of the 6 mean PC scores were higher among women in cluster 2 than women in cluster 3, consistent with their GM chemical concentrations generally being between those of women in clusters 1 and 3. Women in cluster 3 had the highest average PC2 scores; both cluster 3 and PC2 were characterized by higher than average concentrations of MBzP, MiBP, and 3-phenoxybenzoic acid.

Using multinomial logistic regression and after adjustment for sociodemographic, behavioral, lifestyle, and perinatal factors, both race and consumption of fruits and vegetables were associated with membership in cluster 1, which was characterized by higher concentrations of most phenols, three phthalates, several metals, organophosphate and organochlorine pesticides, PCBs, and several PFAS. Specifically, black women were less than half as likely (OR: 0.42; 95% CI: 0.18, 0.99) to be in cluster 1 than white women (Table

3, Table S6). We also found that women who reported consuming fresh fruits and vegetables daily were more than two-times as likely to belong to cluster 1 (OR: 2.33; 95% CI: 1.33, 4.09) than women who did not consume fresh fruit and vegetables daily. Compared to married women, women who were not married were about half as likely (OR: 0.52; 95% CI: 0.23, 1.19) to be in cluster 2, which was characterized by the highest urinary concentrations of MBZP and MiBP among the three clusters and intermediary concentrations of most other biomarker concentrations. The other sociodemographic, behavioral, lifestyle, and perinatal variables were relatively weak predictors of cluster membership (i.e., $0.5 < ORs < 1.5$).

Using multivariable linear regression, and after adjustment for other sociodemographic, behavioral, lifestyle, and perinatal factors, we observed that black women had lower PC1 scores than white women ($\beta = -0.78$, 95% CI: −1.22, −0.34) (Table 4). This indicates that compared to white women, black women in our study had lower concentrations of biomarkers that were most strongly correlated with PC1. Additionally, maternal BMI (β per SD increase in BMI = −0.48, 95% CI: −0.64, −0.33), parity (nulliparous vs multiparous β = 1.08, 95% CI: 0.77, 1.39), and fresh fruits and vegetables consumption (consume daily vs less than daily $\beta = 0.24$, 95% CI: 0.07, 0.54) were associated with PC1 scores. PC2 scores were inversely associated with women's age at delivery ($\beta = -0.78$, 95% CI: −1.22, −0.34). Being married vs unmarried ($\beta = 0.75$, 95% CI: 0.31, 1.19) and each SD increase in age at delivery ($\beta = 0.69$, 95% CI: 0.52, 0.87) were associated with higher PC3 scores. Finally, consuming fresh fruits and vegetables daily was associated with PC6 scores ($\beta = -0.50$, 95% CI: −0.73, −0.27).

DISCUSSION

We investigated the profiles and predictors of exposure to chemical mixtures among pregnant women from Cincinnati, Ohio. We found that chemical concentrations within structurally, commercially, or industrially related classes were more strongly correlated than concentrations of chemicals in different classes. We identified several profiles of chemical exposure using both *k*-means clustering and PCA. Specifically, we observed three clusters of pregnant women with distinct chemical concentration profiles. In addition, we were able to explain the majority the variance in chemical concentrations with 6 PCs. We found that scores from the first two PCs significantly varied by cluster. Some sociodemographic, behavioral, lifestyle, and perinatal variables predicted cluster membership and PC scores.

While gestation is recognized as an especially vulnerable period of development, we are aware of only two previous studies that characterized the profiles of gestational chemical mixture exposure. In a cohort of 728 pregnant women from the INMA Sabadell cohort in Spain, Robinson et al. examined pairwise correlations between 43 environmental chemical biomarkers. Similar to the results of our analysis, they reported that biomarkers of chemicals with similar structures or commercial/industrial uses were more strongly correlated than unrelated chemicals. In their study, 1 or 2 individual principal components explained the majority of the variance for specific classes of chemicals.[22] Another study conducted among 1744 pregnant women in the pan-Canadian MIREC cohort also found similar patterns of correlations among 28 environmental chemicals.[21] The pattern of findings from their PCA was similar to our own and individual PCs explained most of the variance for chemical

concentrations in the same class. For example, the first principal component explained the most of the variance of organochlorine persistent pesticide concentrations and the second principal component explained most of the variance in the phthalates.[21]

We used two different dimension reduction techniques to identify profiles of chemical exposure in an effort to develop new metrics to characterize environmental chemical mixture exposures among pregnant women. Some aspects of the profiles identified by *k*-means clustering and PCA were similar. For example, PC1 and PC2 closely follow patterns of exposure identified using *k*-means clustering. Other principal components did not follow cluster profiles as closely. As noted previously, while many chemicals concentrations were highest in cluster 1, medium in cluster 2, and lowest in cluster 3, some chemicals deviated from this pattern. For instance, lead, BDE-47, and cotinine concentrations were highest in cluster 3, medium in cluster 2, and lowest in cluster 1. In addition, the PCA identified this difference as well, with PC3 having higher loadings for these three chemicals than PC1, which tended to reflect the chemicals with the highest concentration in cluster 1.

The pattern of correlations we observed between chemical concentrations could be due to their combined use in some commercial and industrial products or historical distribution into the environment. For instance, some chemicals are used in the same products (e.g., parabens and some phthalates in personal care products), while other chemicals were previously sold as commercial mixtures and widely distributed in the environment (e.g., PCBs).[42,43] We speculate that the degree of correlation between unrelated chemicals could be due to product formulations, sociodemographic factors, and personal behaviors. However, we were not able to confirm this because we did not have information about the formulation or use of specific products or detailed surveys of behavior and diet. Future studies would benefit from examining product use and behavioral factors as predictors of chemical mixture exposure.

These results suggest that previously identified factors associated with individual chemical exposures are also associated with exposure to chemical mixtures. For instance, similar to previous studies showing that whites have higher urinary triclosan concentrations than blacks,[44] white women in this cohort had higher PC1 scores, which explained most of the variance for urinary triclosan concentrations in our analysis. Furthermore, fruit and vegetable intake was predictive of high PC6 scores, which also explained the majority of the variance in DAP concentrations in the PCA. Additionally, parity was predictive of PC1 scores, which explained most of the variance in OC pesticides and is consistent with previous work showing that nulliparous women have higher serum OC pesticide concentrations than multiparous women.[45] By identifying factors associated with multiple chemical exposures, future epidemiological studies can select appropriate confounders when examining associations between mixtures and human health. Moreover, public health interventions could be targeted to groups most at risk of chemical mixture exposure.

Overall, the profiles of chemical exposures among these pregnant women were qualitatively similar to both *k*-means clustering and PCA, indicating that our results were not sensitive to the models we chose. However, the two methods produce metrics of chemical mixture exposure with unique strengths and limitations. The clusters allow for easily interpretable profiles of cumulative environmental chemical exposure that could be used to predict health

outcomes (e.g., women in cluster 2 were more likely to disease than women in cluster 1). However, it is not possible to examine the dose–response of the cluster with respect to disease outcome. Additionally, *k*-means calculates the centroid of each cluster using the average of all data points in the cluster. Therefore, outliers can bias the *k*-means results if the sample size is small and a single data point drives a cluster's centroid value.[46]

PC regression can be used to investigate the risk of disease with increasing levels of each individual PC, which reflect cumulative exposure to a weighted combination of chemicals. By design individual PCs are not correlated with each other, reducing the potential for multicollinearity. However, interpreting PC scores can be challenging since the scores reflect a weighted sum of chemical concentrations. Future studies using the HOME Study could use these specific clusters or PC scores as categorical or continuous measures of exposure, respectively, to investigate the impact of cumulative chemical exposures on a variety of childhood outcomes such as birth weight, body mass index, or neurodevelopmental disorders. Such results would need to be cautiously interpreted and replicated in other cohorts because the patterns of chemical exposure used to derive clusters or PC scores may be unique to each study.

Our study has some additional limitations. First, there is the potential for misclassification of some chemical exposures. This misclassification is likely greater for the nonpersistent chemicals than persistent chemicals because of their shorter biological half-lives and the episodic nature of exposure to these nonpersistent chemicals. While we attempted to reduce exposure misclassification by averaging up to two biomarker concentrations (>95% of women), it is possible that non-differential exposure misclassification reduced our precision to accurately distinguish exposure profiles to some chemicals in the mixture. Second, our study participants were enrolled from a single U.S. city in the early 2000s and may not be generalizable to other groups of pregnant women or women in other locations or time periods. Reassuringly, concentrations of most chemicals in our study were similar to pregnant women in other U.S.-based studies conducted at the same time.[9,47–50] Additionally, our measures of environmental chemical exposures were collected between 2003 and 2006; thus, we were unable to account for temporal or geographic variations in exposure. Future studies could apply these methods to more recently established birth cohorts in other locations to determine if chemical mixture correlation patterns vary temporally or geographically. Third, we created summary variables for a number of chemical classes or used one chemical as a representative for the whole class (e.g., PCBs and BDE-47); however, individual chemicals within these classes may have distinct patterns which may influence chemical profiles had they been included. Future studies could use the presented or other methods to characterize the patterns of individual PCB or PBDE congener exposures. Fourth, extreme chemical concentration values could have influenced the profiles we observed with both *k*-means and PCA; however, this seems unlikely given our relatively large sample size and the observation that all chemical concentrations had values within 4 SD of the mean. Finally, we used a single imputation method to account for missing exposure data, which would result in us underestimating the standard error in the regression analyses.[51]

These data indicate that pregnant women in the U.S. are exposed to mixtures of environmental chemicals that can be characterized by distinct clusters and principal components. These clusters and principal components were associated with several sociodemographic, behavioral, lifestyle, and perinatal factors. Future studies could use these chemical mixtures profiles to quantify the potential impact of gestational environmental chemical mixture exposures on health outcomes among the HOME Study children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

PCBs	polychlorinated biphenyls
PBDEs	polybrominated diphenyl ethers
PFAS	Perfluoroalkyl substances
CCHMC	Cincinnati Children’s Hospital Medical Center
CDC	Centers for Disease Control and Prevention
MBP	mono-*n*-butyl-phthalate
MBzP	monobenzyl phthalate
MCPP	mono(3-carboxypropyl) phthalate
MEP	monoethyl phthalate
MiBP	monoisobutyl phthalate
DEHP	di(2-ethylhexyl) phthalate
MEHP	mono-2-ethylhexyl phthalate
MEHHP	mono-2-ethyl-5-hydroxyhexyl phthalate
MEOHP	mono-2-ethyl-5-oxohexyl phthalate
MECPP	mono-2-ethyl-5-carboxypentyl phthalate
As	arsenic

Cd	Cadmium
OC	organochlorine
DAP	dialkyl phosphate metabolites
LOD	limit of detection
BMI	body mass index
CCC	cubic cluster criterion
GM	geometric mean
PCA	principal component analysis
PC	principal component
PFOS	perfluorooctanesulfonate
PFHxS	perfluorohexanesulfonate
DDE	dichlorodiphenyldichloroethylene

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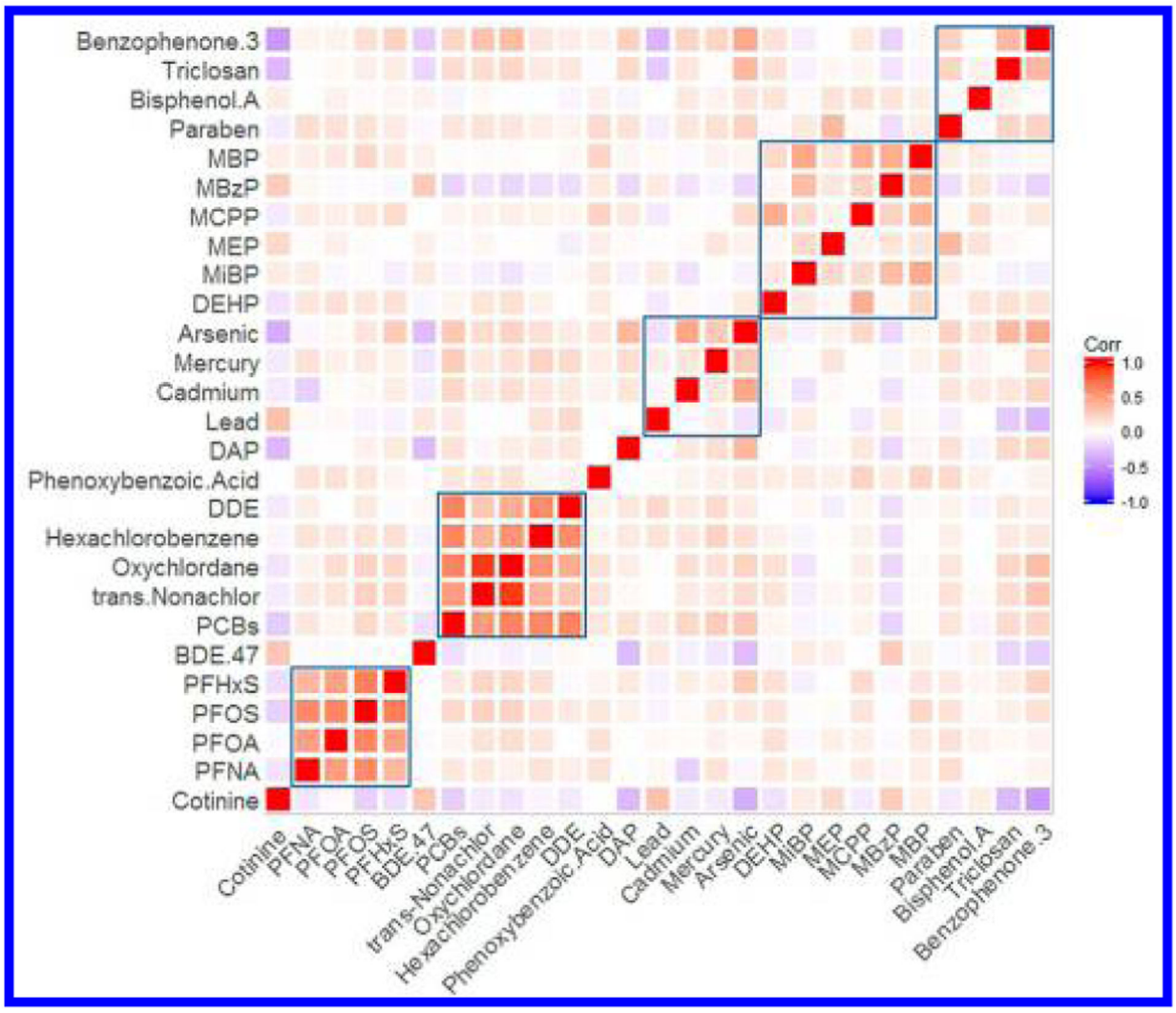

Figure 1.

Heat map of pairwise correlations between chemical concentrations among pregnant women in the HOME Study. Red indicates positive correlations, white represents no correlation, and blue indicates negative correlations. The correlation heatmap was created using $\log_{10}$-normalized urinary or serum chemical concentrations. All urinary and serum chemical concentrations were creatinine and lipid standardized, respectively. The paraben summary variable (∑parabens) is the molar sum of methylparaben, propylparaben, and butylparaben. The paraben summary variable (∑parabens) is the molar sum of methylparaben, propylparaben, and butylparaben. The di(2-ethylhexyl) phthalate summary variable (∑DEHP) is the molar sum of its urinary metabolites MEHP, MEHHP, MEOHP, and MECPP. The organophosphate pesticides summary variable (∑DAP) is the molar sum of DEDTP, DEP, DETP, DMDTP, DMP, and DMTP. The polychlorinated biphenyls summary variable ($\sum_4$PCBs) is the sum of PCB 138/158, PCB 118, PCB 153, and PCB 180.

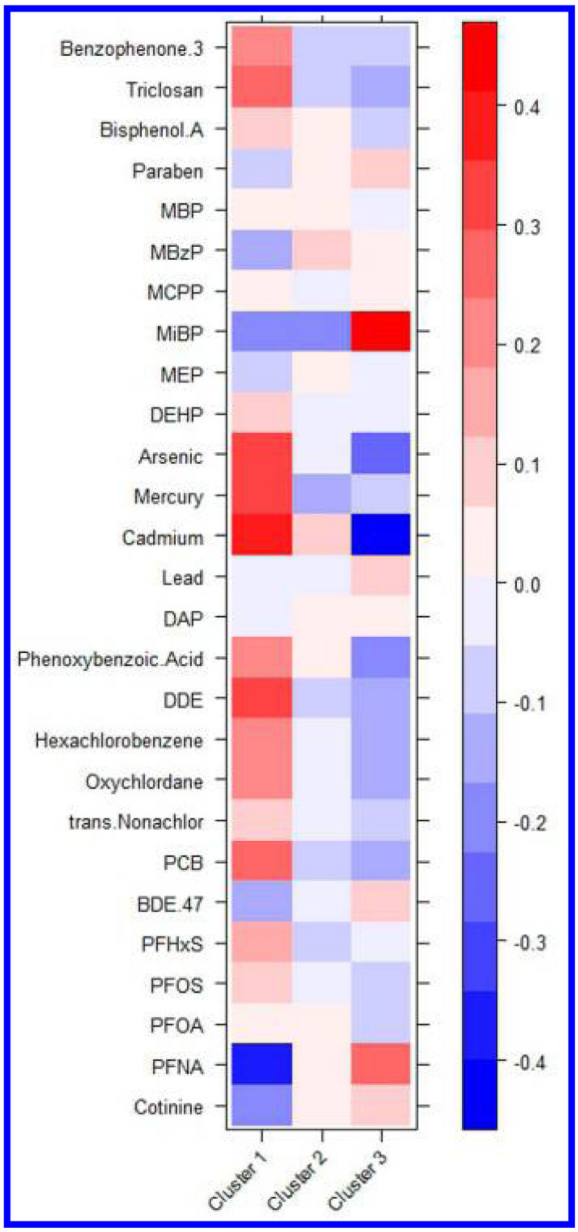

Figure 2.

Heat map of mean chemical concentration z-scores by cluster membership among pregnant women in the HOME Study. Cluster 1, 2, and 3 sample sizes were 106, 158, and 125, respectively. Red indicates higher than average chemical concentrations, white represents average chemical concentrations, and blue indicates lower than average chemical concentrations. The paraben summary variable (∑parabens) is the molar sum of methylparaben, propylparaben, and butylparaben. The paraben summary variable (∑parabens) is the molar sum of methylparaben, propylparaben, and butylparaben. The di(2-ethylhexyl) phthalate summary variable (∑DEHP) is the molar sum of its urinary metabolites MEHP, MEHHP, MEHOP, and MECPP. The organophosphate pesticides summary variable (∑DAP) is the molar sum of DEDTP, DEP, DETP, DMDTP, DMP, and DMTP. The

polychlorinated biphenyls summary variable ($\sum_4$PCBs) is the sum of PCB 138/158, PCB 118, PCB 153, and PCB 180.

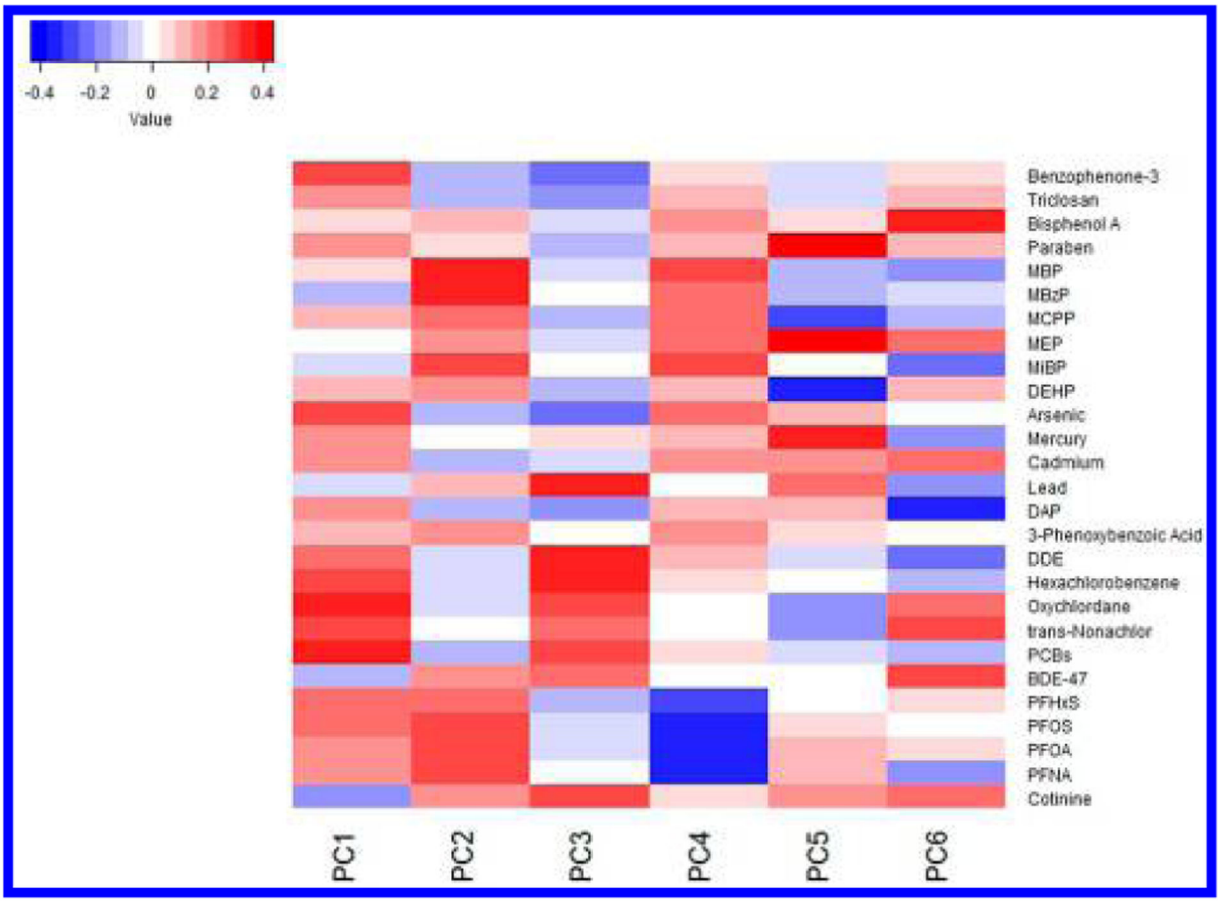

Figure 3.

Heat map of loading factors from principal component analysis of chemical concentrations among pregnant women in the HOME Study. Red indicates the range of positive loading factors and blue indicates the range of negative loading factors. The PCA was constrained to 6 principal components. The paraben summary variable (∑parabens) is the molar sum of methylparaben, propylparaben, and butylparaben. The arsenic summary variable (∑arsenic) is the summed concentration of concentrations of As III, DMA, MMA, and As V. The di(2-ethylhexyl) phthalate summary variable (∑DEHP) is the molar sum of the metabolites MEHP, MEHHP, MEOHP, and MECPP. The organophosphate pesticides summary variable (∑DAP) is the molar sum of DEDTP, DEP, DETP, DMDTP, DMP, and DMTP. The polychlorinated biphenyls summary variable (∑4PCBs) is the sum of PCB 138/158, PCB 118, PCB 153, and PCB 180.

Table 1.

Univariate Characteristics of Urinary, Blood, or Serum Chemical Concentrations among Pregnant Women from the HOME Study[a]

Chemical	Chemical Class	Matrix	*N*	LOD	GeometricMean	25th, 75th Percentile
Benzophenone-3 (ng/mL)	Phenols	Urine	389	1.7	32.8	6.9,124.0
Triclosan (ng/mL)	Phenols	Urine	389	0.4	22	7.5, 50
Bisphenol A (ng/mL)	Phenols	Urine	389	0.4	2.1	1.4, 3.0
∑Parabens (ng/mL)	Phenols	Urine	389	NA	267	119, 692
Mono-n-butyl-phthalate (MBP) (ng/mL)	Phthalates	Urine	389	0.6	26	17, 37
Monobenzyl phthalate (MBzP) (ng/mL)	Phthalates	Urine	389	0.3	10	5, 16
Mono(3-carboxypropyl) phthalate (MCPP) (ng/mL)	Phthalates	Urine	389	0.2	2.3	1.6, 3.3
Monoisobutyl-phthalate (MiBP) (ng/L)	Phthalates	Urine	389	0.3	4.7	3.0, 7.6
Monoethyl phthalate (MEP) (ng/mL)	Phthalates	Urine	389	0.8	140	69, 283
ΣDEHP (ng/mL)	Phthalates	Urine	389	NA	91	49, 147
ΣArsenic (ng/mL)	Metals	Urine	311	NA	5.3	3.6, 7.8
Mercury (ng/mL)	Metals	Blood	387	0.14	0.6	0.4, 1.0
Cadmium (ng/mL)	Metals	Urine	311	0.07	0.2	0.1, 0.3
Lead (wg/dL)	Metals	Blood	368	0.18	0.7	0.5, 0.8
∑DAP (ng/mL)	Organophosphate Pesticides	Urine	388	NA	49	22, 114
3-Phenoxybenzoic Acid (ng/mL)	Pyrethroid Pesticides	Urine	388	0.06	0.4	0.2, 0.7
p ‘p’-dichlorodiphenyldichloroethylene (DDE) (ng/g lipid)	Organochlorine Pesticides	Serum	365	4.0	76	54, 100
Hexachlorobenzene (HCB) (ng/g lipid)	Organochlorine Pesticides	Serum	310	3.1	7.2	5.7, 9.0
Oxychlordane (ng/g lipid)	Organochlorine Pesticides	Serum	302	2.1	5.1	3.6, 7.4
trans-Nonachlor (ng/g lipid)	Organochlorine Pesticides	Serum	317	2.2	7.7	5.1, 11.8
Σ_4PCB (ng/g lipid)	Polychlorinated Biphenyls	Serum	364	NA	31	21, 34
Polybrominated diphenyl ether (BDE-47) (ng/g lipid)	Polybrominated Diphenyl Ethers	Serum	365	0.9	20	11, 34
Perfluorohexanesulfonate (PFHxS) (ng/mL)	Perfluoroalkyl Substances	Serum	342	0.1	1.5	0.9, 2.4
Perfluorooctanesulfonate (PFOS) (ng/mL)	Perfluoroalkyl Substances	Serum	342	0.1	13	10, 18
Perfluorooctanoate (PFOA) (ng/mL)	Perfluoroalkyl Substances	Serum	342	0.1	5.5	3.9, 7.8
Perfluorononanoate (PFNA) (ng/mL)	Perfluoroalkyl Substances	Serum	342	0.1	0.9	0.7, 1.2
Cotinine (ng/mL)	Tobacco Smoke Exposure	Serum	387	0.015	0.1	<LOD 0.3

[a]The paben summary variable (∑parabens) is the molar sum of methylparaben, propylparaben, and butylparaben.

[b] The arsenic summary variable (∑arsenic) is the summed concentration of concentrations of As III, DMA, MMA, and As V.

[c] The di(2-ethylhexyl) phthalate summary (∑DEHP) variable is the molar sum of its urinary metabolites MEHP, MEHHP, MEOHP, and MECPP.

[d] The organophosphate pesticides summary variable (∑DAP) is the molar sum of DEDTP, DEP, DETP, DMDTP, DMP, and DMTP.

[e] The polychlorinated biphenyls summary variable ($\sum_4$PCBs) is the sum of PCB 138/158, PCB 118, PCB 153, and PCB 180.

Table 2.

Mean Principal Component Scores for Women in Each Cluster for the Six Principal Components That Explained 50% of the Variation in Chemical Concentrations among Pregnant Women in the HOME Study[a]

Principal Component	Mean PC Score Cluster 1, *N* = 106	Mean PC Score Cluster 2, *N* = 158	Mean PC Score Cluster 3, *N* = 125	p-value[b]
PC1	0.72	−0.12	−0.46	0.0001
PC2	−0.44	0.00	0.37	<0.0001
PC3	−0.01	−0.02	0.04	0.93
PC4	0.20	−0.05	−0.11	0.23
PC5	−0.01	0.03	−0.03	0.91
PC6	0.01	0.11	−0.15	0.17

[a]PC scores were calculated by multiplying the original chemical concentration z-scores by that chemical's PCA loading factor for each principal component.

[b]*p*-values were calculated by comparing mean PC scores using a one-way ANOVA with 2 degrees of freedom.

Table 3.

Adjusted Odds of Cluster Membership among Pregnant Women According to Sociodemographic, Behavioral, and Lifestyle Variables among Pregnant Women in the HOME Study (N = 380)[a]

Variable	Cluster 1 N	Cluster 2 N	Cluster 3 N	Cluster 1 vs 3 OR (95% CI)	Cluster 2 vs 3 OR (95% CI)
Maternal Race					
White	72	94	70	ref	ref
Black	22	50	46	0.42 (0.18, 0.99)	0.81 (0.39, 1.69)
Other	11	7	8	1.35 (0.49, 3.72)	0.72 (0.24, 2.13)
Marital Status					
Married	74	100	73	ref	ref
Not Married	31	51	51	0.75 (0.30, 1.84)	0.52 (0.23, 1.19)
Household Income	105	151	124	0.92 (0.63, 1.35)	0.88 (0.62, 1.26)
Maternal Education					
Greater than High School	85	108	94	ref	ref
High School or less	20	43	30	1.31 (0.57, 3.05)	2.00 (0.97, 4.13)
Maternal Age at Delivery	105	151	124	0.88 (0.61, 1.29)	1.09 (0.79, 1.50)
Maternal Body Mass Index **Parity**	105	151	124	0.94 (0.70, 1.26)	1.05 (0.81, 1.34)
Multiparous	55	88	67	ref	ref
Nulliparous	50	63	57	0.83 (0.46, 1.47)	0.89 (0.53, 1.50)
Fish Consumption					
Any	91	130	102	ref	ref
None	14	21	22	0.76 (0.36, 1.61)	0.85 (0.44, 1.67)
Fruit and Veg Consumption					
Less than daily	50	95	84	ref	ref
Daily	55	56	40	2.33 (1.33, 4.09)	1.30 (0.77, 2.19)

[a]Cluster 1, 2, and 3 sample sizes were 105, 151, and 124.

[b]The adjusted analysis includes all sociodemographic, behavioral, lifestyle, and perinatal variables listed in the table in the same model.

[c]Odds ratios for maternal age (SD: 5.8 years), household income (SD: $42,238), and maternal BMI (SD: 6.8 kg/m^2) have been scaled so that the adjusted OR is per standard deviation change in those variables.

Table 4.

Adjusted Differences in Principal Component Scores among Pregnant Women According to Sociodemographic, Behavioral, and Lifestyle Variables in the HOME Study *(N* = 380)[a]

Variable	PC1 β (95% CI)	PC2 β (95% CI)	PC3 β (95% CI)	PC4 β (95% CI)	PC5 β (95% CI)	PC6 β (95% CI)
Maternal Race						
White	ref	ref	ref	ref	ref	ref
Black	−0.78 (−1.22, −0.34)	−0.51 (−1.0, −0.01)	1.05 (0.65, 1.45)	0.16 (−0.27, 0.59)	0.84 (0.5, 1.18)	−0.36 (−0.7, −0.02)
Other	0.40 (−0.19, 0.99)	0.18 (−0.48, 0.84)	1.12 (0.58, 1.65)	0.38 (−0.19, 0.96)	0.35 (−0.11, 0.8)	−0.60 (−1.06, −0.15)
Marital Status						
Married	ref	ref	ref	ref	ref	ref
Not Married	−0.19 (−0.68 0.29)	0.38 (−0.17, 0.92)	0.75 (0.31, 1.19)	0.04 (−0.43, 0.51)	0.22 (−0.16, 0.59)	0.32 (−0.05, 0.7)
Household Income	0.15 (−0.06 0.36)	−0.04 (−0.28, 0.19)	−0.27 (−0.46, −0.08)	−0.16 (−0.36, 0.04)	0.26 (0.1, 0.42)	−0.08 (−0.24, 0.08)
Maternal Education						
Greater than High School	ref	ref	ref	ref	ref	ref
High School or less	−0.01(−0.44 0.43)	0.53 (0.04, 1.02)	0.36 (−0.04, 0.75)	0.16 (−0.26, 0.58)	0.36 (0.03, 0.7)	0.09 (−0.25, 0.42)
Maternal Age at Delivery	0.95 (0.75 1.14)	−0.27 (−0.49, −0.05)	0.69 (0.52, 0.87)	0.20 (0.01, 0.39)	−0.05 (−0.2, 0.09)	0.06 (−0.09, 0.21)
Maternal Body Mass Index	−0.48 (−0.64−0.33)	0.14 (−0.03, 0.31)	−0.16 (−0.3,− 0.02)	−0.13 (−0.28, 0.02)	−0.19 (−0.3, −0.07)	0.04 (−0.07, 0.16)
Parity						
Multiparous	ref	ref	ref	ref	ref	ref
Nulliparous	1.08 (0.77 1.39)	0.18 (−0.16, 0.53)	0.07 (−0.21, 0.35)	−0.26 (−0.56, 0.04)	0.53 (0.29, 0.77)	−0.32 (−0.56, −0.08)
Fish Consumption						
Any	ref	ref	ref	ref	ref	ref
None	−0.39 (−0.79 0.02)	−0.17 (−0.63, 0.28)	−0.19 (−0.56, 0.18)	−0.17 (−0.56, 0.23)	−0.57 (−0.88, −0.26)	0.40 (0.09, 0.71)
Fruit and Veg Consumption						
Less than daily	ref	ref	ref	ref	ref	ref
Daily	0.24 (−0.07 0.54)	−0.22 (−0.56, 0.12)	0.01 (−0.27, 0.28)	0.06 (−0.23 0.36)	0.02 (−0.22, 0.25)	−0.50 (−0.73, −0.27)

[a]PC scores were calculated by multiplying the original chemical concentration z-scores by that chemical's PCA loading factor for each principal component.

[b]The adjusted analysis includes all sociodemographic, behavioral, lifestyle, and perinatal variables listed in the table in the same model.

[c]Odds ratios for maternal age (SD: 5.8 years), household income (SD: $42,238), and maternal BMI (SD: 6.8 kg/m^2) have been scaled to reflect a standard deviation change.

[d] Example interpretation: When adjusting for all other sociodemographic, behavioral, lifestyle, and perinatal factors black women had on average 0.78 (95% CI: −1.22, −0.34) lower PC1 scores as compared to white women.