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Disparities in chemical exposures among pregnant women and neonates by socioeconomic and demographic characteristics: A nontargeted approach

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A B S T R A C T

Background: Exposure to environmental chemicals during pregnancy adversely affects maternal and infant health, and identifying socio-demographic differences in exposures can inform contributions to health inequities.

Methods: We recruited 294 demographically diverse pregnant participants in San Francisco from the Mission Bay/Moffit Long (MB/ML) hospitals, which serve a primarily higher income population, and Zuckerberg San Francisco General Hospital (ZSFGH), which serves a lower income population. We collected maternal and cord sera, which we screened for 2420 unique formulas and their isomers using high-resolution mass spectrometry using LC-QTOF/MS. We assessed differences in chemical abundances across socioeconomic and demographic groups using linear regression adjusting for false discovery rate.

Results: Our participants were racially diverse (31% Latinx, 16% Asian/Pacific Islander, 5% Black, 5% other or multi-race, and 43% white). A substantial portion experienced financial strain (28%) and food insecurity (20%) during pregnancy. We observed significant abundance differences in maternal (9 chemicals) and cord sera (39 chemicals) between participants who delivered at the MB/ML hospitals versus ZSFGH. Of the 39 chemical features differentially detected in cord blood, 18 were present in pesticides, one per- or poly-fluoroalkyl substance (PFAS), 21 in plasticizers, 24 in cosmetics, and 17 in pharmaceuticals; 4 chemical features had unknown sources. A chemical feature annotated as 2,4-dichlorophenol had higher abundances among Latinx compared to white participants, those delivering at ZSFGH compared to MB/ML, those with food insecurity, and those with financial strain. Post-hoc QTOF analyses indicated the chemical feature was either 2,4-dichlorophenol or 2,5-dichlorophenol, both of which have potential endocrine-disrupting effects.

Conclusions: Chemical exposures differed between delivery hospitals, likely due to underlying social conditions faced by populations served. Differential exposures to 2,4-dichlorophenol or 2,5-dichlorophenol may contribute to disparities in adverse outcomes.

1. Introduction

Exposure to environmental chemicals during pregnancy can have long-term impacts on maternal and infant health (Perera and Herbstman, 2011). Given the numerous physiologic changes that occur during pregnancy, environmental chemicals can have unique toxicity during this period. For instance, exposure to endocrine-disrupting chemicals during gestation has been linked with later breast cancer occurrence (Birnbaum and Fenton, 2003; Terry et al., 2019). Chemical exposures during pregnancy can detrimentally affect infant health and child development, including delays in neurodevelopment (Sapbamrer and Hongsibsong, 2019; Ejaredar et al., 2015; Liu et al., 2019; Rochester et al., 2018; Lam et al., 2017) and metabolic disorders (Gutiérrez-Torres et al., 2018; Halldorsson et al., 2012; Mendez et al., 2011; Valvi et al., 2013; Zarean et al., 2018).

In the United States, routine biomonitoring tracks a selection of harmful chemicals to which pregnant people are exposed (Sobus et al., 2015). However, over 90% of high production volume chemicals are not part of routine biomonitoring, and the extent of human exposure to many of these chemicals is not known (Wang et al., 2021; Jiang et al., 2021; Egeghy et al., 2012; Panagopoulos Abrahamsson et al., 2021). Characterizing exposure among pregnant women is critical to identifying potential harms to maternal and fetal health. Furthermore, characterizing the distribution of exposure to these chemicals across sociodemographic and economic groups is critical to identify differential exposure patterns that may play a role in shaping disparities in maternal

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and infant health.

Advancements in nontargeted analysis have made screening for a larger number of chemicals more feasible (Sobus et al., 2018; Andra et al., 2017; Plassmann et al., 2018). Therefore, to improve our understanding of the exposome among pregnant people, we used nontargeted analysis to characterize environmental chemical exposures among mothers and their neonates in San Francisco (Wang et al., 2021; Panagopoulos Abrahamsson et al., 2021). This approach allows us to avoid the traditional *a priori* specification of chemicals to test for and enables us to systematically characterize chemical exposures in a more comprehensive way. We collected maternal and cord sera from mothers and their newborns at delivery in three San Francisco hospitals and linked biospecimens to participant surveys and medical records. We then evaluated whether chemical abundances detected in maternal and cord sera differed by socioeconomic and demographic characteristics. This allowed us to evaluate whether disparities in exposure to certain chemicals exist and if so, to identify groups whose exposure profiles place them at increased risk for adverse health outcomes.

2. Data and methods

2.1. Study population and sample collection

We recruited 294 participants from 2014 to 2019 during their second trimester from the Mission Bay and Moffit Long Hospitals (MB/ML), which serve predominantly privately insured patints, and Zuckerberg San Francisco General Hospitals (ZSFGH), a safety net hospital that serves primarily publicly insured patients as part of our ongoing Chemicals In Our Bodies (CIOB) pregnancy cohort study. We administered interview questionnaires at the second trimester, collected maternal and neonatal biospecimens at delivery, and linked this participant information to their medical records. The majority of maternal samples were collected before delivery (N = 260), but some were collected shortly after delivery (N = 34). All cord samples were collected after delivery. No preservatives were added to the samples, which were collected in glass tubes. Women were eligible for recruitment if they were English or Spanish-speaking, over 18 years old, and carrying a singleton pregnancy that was between 13 and 27 weeks gestation at the recruitment visit.

The study protocol was approved by the Institutional Review Boards of the University of California, San Francisco (IRB number 13–12160).

2.2. Nontargeted chemical analysis

We used nontargeted high resolution mass spectrometry to measure chemicals in maternal and cord sera. After biospecimen collection, samples were stored at −80 °C in freezers at UCSF until they were transported on dry ice to the California Department of Toxic Substances Control Environmental Health Laboratory in Berkeley, California. Maternal and neonatal sera samples were prepared according to the following steps: 1). Aliquots of 250 μ L were spiked with 25 μ L 100 ng/L surrogate standard mixture of 100 ng/mL Perfluoro-[1,2,3,4–13C4] octanoic acid (negative mode) and DL-cotinine (methyl-D3)) and triphenyl phosphate D15 (positive mode), 2). 2 mL 0.1% formic acid methanol solution were added to induce protein precipitation, 3). The samples were then centrifuged and the supernatant was transferred to clean glass tubes, and 4). The samples were then evaporated with a gentle stream of nitrogen and reconstituted to a volume of 150 μ L with methanol. The blank samples (LCMS grade water) and in-house spiked QC samples were equivalently treated. All samples were mixed and stored at 4 °C until liquid chromatography quadrupole time-of-flight/mass spectrometry (LC-QTOF/MS) was performed using an Agilent UPLC coupled to an Agilent 6550 QTOF (Agilent Technologies, Santa Clara, CA) in both positive and negative electrospray ionization modes. Specifically, 10 μL of each sample extract were injected sequentially into an Agilent 1290 UPLC interfaced with an iFunnel 6550 QTOF-MS system for TIC mass spectra acquisition in both negative (ESI−) and positive (ESI+) ionization mode.

We acquired full scan accurate mass spectra in the range of 100–1000 Da with resolving power of 40,000 and a mass accuracy of <5 ppm. The QTOF was calibrated, and the mass accuracy was corrected with reference standards of reference masses 112.985587 and 1033.988109 for negative mode, and 121.050873 and 922.009798 for positive mode before each batch during the run. An Agilent Eclipse Plus C18 column (2.1 × 100 mm, 1.8 μm) was used with 5 mM ammonium acetate in water (0.1% methanol) as gradient A and 5 mM ammonium acetate in methanol with 10% water as gradient B. The gradient flow was set to be 0.3 mL/min with the increase of the organic phase from 10% to 100% over 15 min followed by a 4 min equilibration at 100%. Two technical replicates were analyzed for each sample. Two blank samples and two quality control samples with two replicates were also analyzed together within one batch.

Water blanks, matrix blanks, and matrix spike blanks were included in each batch. Mass error and retention time shifts of the internal standards and spiked PFAS (for ESI - mode) and OPFR (for ESI + mode) mixes were monitored for quality control and observed to be within 5 ppm and 0.1 min respectively. Internal standards peak intensity in each sample was used for normalization. We used Agilent MassHunter Profinder to process data and extract features from the raw total ion chromatograms (TIC). We processed the raw MS TIC data files using Agilent MassHunter Profinder software (version B.08.00) with the raw molecular feature extraction (MFE), with relaxed binning and alignment parameters of a 0.5 min RT window and a 50 ppm + 2 mDa mass window), and target MFE algorithms (with a much narrower window of 5 ppm) to extract compound features recursively across the batch data files to reduce false positive hits. The extracted features were then aligned (RT correction window = 5% + 0.5 min, mass correction window = 10 ppm + 2 mDa, RT alignment window = 0.3 min) throughout the whole data set using the Agilent Mass Profiler Professional software (MPP, version 12.06.01). Features that 1). Only appeared once in the data set and 2). Did not have significantly higher (2-fold) concentrations in samples than in blanks were removed. The resulting features were then screened against our database for human exposure studies (described in detail previously (Wang et al., 2021)) and the HUMANBLOOD database in EPA's Chemistry Dashboard based on the spectral information (mass, isotopic abundance and patterns, as well as adduct ions) using MPP with a mass tolerance window of 5 ppm + 0.01 mDa and a score >70 as the threshold (isotopic abundance and patterns are taken into account in the software scoring system). Adducts of [M+H]+, [M+Na]+, [M+K]+ and [M + NH4]+ were examined for positive mode, whereas [M-H]- and [M + CH3COO]- species were examined for negative mode. Additionally, for formulas containing Cl and Br we did a visual inspection to see whether we could detect the unique isotopic patterns of Cl and Br. However, this was limited to the features that had sufficiently high abundances that allowed for the detection of the unique isotopic patterns. The raw data is available on Metabolomics Workbench with data ID 3403.

2.3. Data processing

We imputed values below the limit of detection by fitting a normal distribution to the log-10 transformed abundances for each chemical feature and simulating random values between 0 and the limit of detection (Ejaredar et al., 2015), which was described in detail previously (Panagopoulos Abrahamsson et al., 2021). We also implemented a batch correction, as the samples were analyzed within two shipments, with approximatately 15 batches in each. The batches were not randomized by date of collection, but the maternal and cord paired samples were randomized within batches. We used ComBat to correct for batch effects both within and between shipments. Correction also was made for potential shifts in retention time and differences in peak alignment in order to combine the data across the two shipments. Features were

indexed by their formulas and the number of isomers and matched across the shipments. Any features that were present in only one of the datasets were removed. Additionally, any matched features whose retention time differed by more than 0.5 min or whose mass difference was more than 15 ppm were removed. Finally, we removed electrospray ionization adducts by removing any features that had i) correlations greater than 0.5 and ii) distinct mass differences consistent with salt ions. A mass accuracy filter of 15 ppm was used for the adduct removal process. This resulted in 685 unique chemical features across the 294 participants (Panagopoulos Abrahamsson et al., 2021).

2.4. Annotation

Detailed description of the annotation process has been previously published (Panagopoulos Abrahamsson et al., 2021). Briefly, we removed chemicals that have been previously detected in human blood as likely endogenous molecules. We used the HUMANBLOOD database from EPA's Chemistry Dashboard to identify these likely endogenous compounds (Williams et al., 2017). We used databases for exogenous chemicals, also from EPA's Chemistry Dashboard, to identify all isomers for the exogenous formulas. We annotated the chemical features using the most likely isomer, which was determined based on ranking all isomers according to the number of available isomers and the number of data sources in the Chemistry Dashboard, the number of PubChem data sources, and the number of publications in PubMed (Abrahamsson et al., 2020). This annotation procedure assumes that the most prevalent isomers are the most studied and have the most information about them. While imperfect, this approach nevertheless provides important diagnostic evidence for the identification of chemical compounds and can be highly informative if there are few isomers for a particular formula or if all potential isomers have similar properties.

2.5. Statistical analysis

We assessed whether there were differences in log-10 abundances between sociodemographic and economic groups in maternal and neonatal serum using linear regression. The independent variables, which included race/ethnicity, age, educational attainment, employment status, nativity, occupation, hospital of delivery, food security, and financial strain, were evaluated separately. No covariates were included. Maternal age and hospital of delivery came from the medical record, while race/ethnicity, educational attainment, employment status, nativity, occupation, food security, and financial strain were collected from questionnaires. To adjust for multiple comparisons, we used the Benjamini-Hochberg false discovery rate with an α-level of 0.1.

3. Results

The majority of our study population was 31 years or older, had a college degree, and was employed at the time of the survey (Table 1). The population was racially and economically diverse, with 43% identifying as white, 31% Latina, 5% Black, 16% Asian or Pacific Islander, and 5% Other or multiple race. Just over half were born in the United States (54%), about 20% were food insecure, and almost 30% experienced financial strain. About two-thirds of the study population delivered at MB/ML hospitals and one-third at ZSFGH.

Among both the maternal and cord samples, we observed the most striking differences between mothers who delivered at MB/ML versus ZSFGH (Fig. 1). There were nine chemicals we defined as significantly different abundances in maternal serum between the ZSFGH and MB/ML participants, five that had higher abundances among ZSFGH participants and four that had higher abundances among MB/ML participants (Fig. 2). The chemical features that had higher abundance in maternal serum among participants who delivered at ZSFGH were 2,4-dichlorophenol (an ingredient in pesticides), diheptyl phthalate (in pharmaceuticals), dicyclohexyl phthalate (a plasticizer), 6-acetoxy-5-hexadecanolide (source unknown), (Z)-hexadec-9-enoic acid (in pharmaceuticals, pesticides, cosmetics, and a plasticizer). The chemical features that had lower abundance in maternal serum of ZSFGH participants compared to MB/ML participants were annotated as (3-methoxyphenyl)methyl propanoate (in pesticides, cosmetics, and a plasticizer), methyl 12-hydroxyoctadecanoate (in pesticides and cosmetics), tetracosanoic acid (in pharmaceuticals, cosmetics, and a plasticizer), peroxydicarbonic acid, and C,C′-ditetradecyl ester (a plasticizer). Overall, 17 chemical features had significantly different abundances in maternal sera across at least one of the sociodemographic groups (Supplemental Figure 1).

Table 1
Descriptive statistics of study participants (N = 294).

Age	N	%
15–25	26	9%
26–30	41	14%
31–35	134	46%
36–47	93	32%
Race/ethnicity		
White	127	43%
Latina	91	31%
Black	14	5%
Asian/PI	47	16%
Other or multiple race	15	5%
Educational attainment		
Less than high school	26	9%
High school diploma or GED	44	15%
Some college course work for credit or AA degree	29	10%
Bachelor's degree (4 years)	195	66%
Employment status		
Not in labor force	53	18%
Employed/Student	222	76%
Unemployed/Other	19	6%
Nativity		
Born in US	160	54%
Not born in US	135	46%
Occupation		
Not in labor force or unknown	91	31%
Health care	50	17%
Research	23	8%
Business or legal	70	24%
Education, arts, or caregiving	32	11%
Cleaning, food, or other service	29	10%
Food insecure		
No	236	80%
Yes	59	20%
Financial strain		
No	214	73%
Yes	81	28%
Hospital		
Mission Bay or Moffit Long	211	72%
Zuckerberg San Francisco General	84	29%

There were 39 chemical features we defined as significantly different abundances in cord serum between babies delivered at ZSFGH versus MB/ML (Figs. 1 and 2). Of these, 17 were present in pharmaceuticals, 18 in pesticides, one PFAS, 21 in plasticizers, and 24 in cosmetics. Four chemical features had unknown sources. Three overlapped with chemical features that had differential abundances in maternal serum by hospital. These were annotated as (3-methoxyphenyl)methyl propanoate (less abundant among ZSFGH participants, and an ingredient in pesticides, cosmetics, and a plasticizer), tetracosanoic acid (less common among ZSFGH participants, and an ingredient in pharmaceuticals, cosmetics, and a plasticizer), 2,4-dichlorophenol (more common among ZSFGH participants, ingredient in pesticides). The directions and magnitudes of the abundance differences in these three chemical features were similar in maternal and cord samples. Overall, 43 chemical features had significantly different abundances in cord sera across at least one of the sociodemographic groups (Supplemental Figure 2).

We found higher abundances of the chemical feature annotated as the pesticide 2,4-dichlorophenol in maternal serum among our Latina

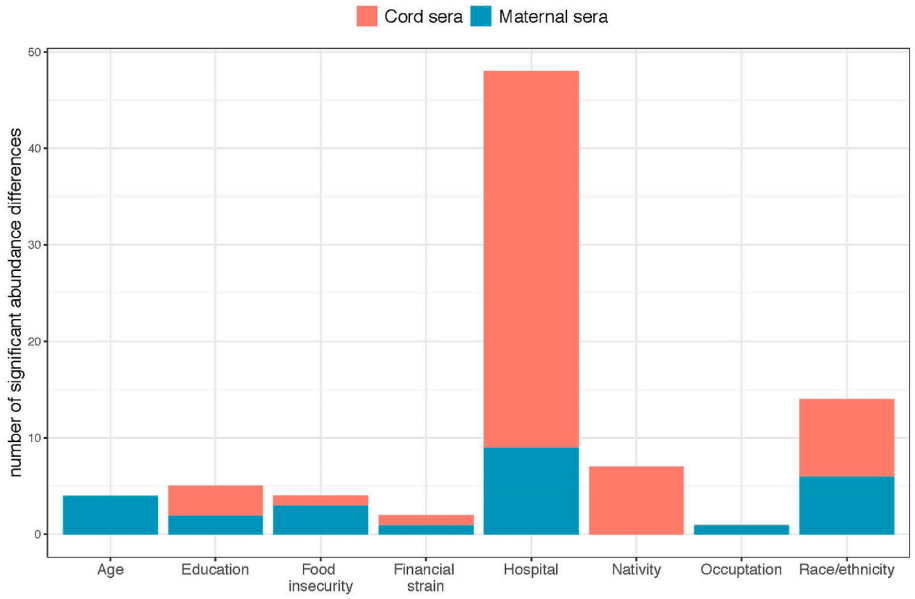

Fig. 1. Number of chemical features with significant abundance differences by socioeconomic and demographic groups in maternal and cord sera. Note: Abundance differences were considered significant at the false discovery rate (FDR) p-value of 0.1.

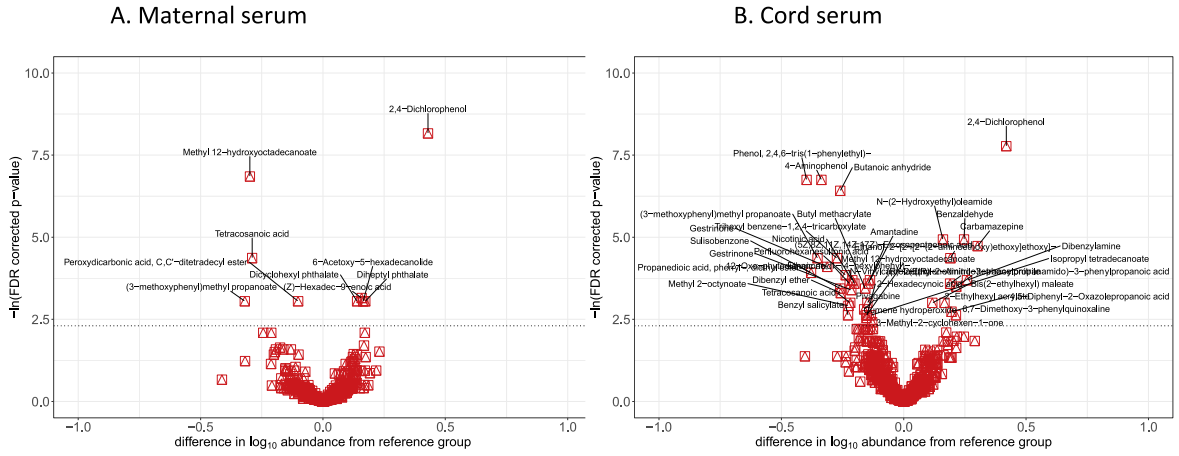

Fig. 2. Abundances differences by hospital of delivery (MB/ML vs. ZSFGH) in maternal and cord serum. A. Maternal serum. B. Cord serum. Note: MB/ML hospitals are the reference group. The dotted line indicates a false discovery rate (FDR) p-value of 0.1. Chemical features with abundance differences significant at the FDR-adjusted level of 0.1 are annotated with their likely names.

participants compared to white participants (Fig. 3). We also observed lower abundances of two PFAS chemicals, perfluorohexanesulfonic acid (PFHxS) and perfluorooctanesulfonic acid (PFOS), as well as lower abundances of chemical features annotated as tetracosanoic acid (in pharmaceuticals, cosmetics, and a plasticizer) and (3-methoxyphenyl) methyl propanoate (in pesticides, cosmetics, and a plasticizer) among Latina compared to white participants. Among Asian participants, we observed higher abundances of perfluoro(2-((6-chlorohexyl)oxy)ethanesulfonic acid), a PFAS chemical. According to our false discovery rate (FDR) cutoff of 0.1, there were no significant differences in abundances among Black or Other race participants compared to white participants in our study.

In the cord serum, we similarly observed higher abundances of the chemical feature annotated as 2,4-dichlorophenol (a pesticide ingredient) and lower abundances of perfluorohexanesulfonic acid (PFHxS) among Latina compared to white participants (Fig. 4). Abundances of chemical features annotated as 4-aminophenol (in pharmaceuticals, pesticides, and cosmetics), nicotinic acid (in pharmaceuticals, pesticides, and cosmetics), trihexyl benzene-1,2,4-tricarboxylate (a plasticizer), and gestrinone (in pharmaceuticals and a plasticizer) were also lower among Latina compared to white participants. Among Asian participants, abundance of the chemical feature annotated as gestrinone (in pharmaceuticals and a plasticizer) was also lower compared to white participants.

We also examined whether maternal and cord sera abundances differed by maternal age, educational attainment, employment status, nativity, occupation, food insecurity, and financial strain (Figs. 5 and 6). Four chemical features had significantly higher abundances in maternal serum among older mothers (Fig. 5). These were annotated as (3-methoxyphenyl)methyl propanoate (present in pesticides, plastics, and cosmetics); valerenic acid (present in pesticides, plastics, and cosmetics); hexadecanoic acid, 1-methylethyl ester (present in pharmaceuticals, pesticides, plastics, and cosmetics); and dopamine quinone (present in pharmaceuticals, plastics, and cosmetics). One chemical feature, annotated as methyl 12-hydroxyoctadecanoate (present in pesticides and cosmetics), had higher abundance in college-educated mothers. One chemical feature with lower abundance in college-educated women was annotated as 2,4-dichlorophenol, a pesticide

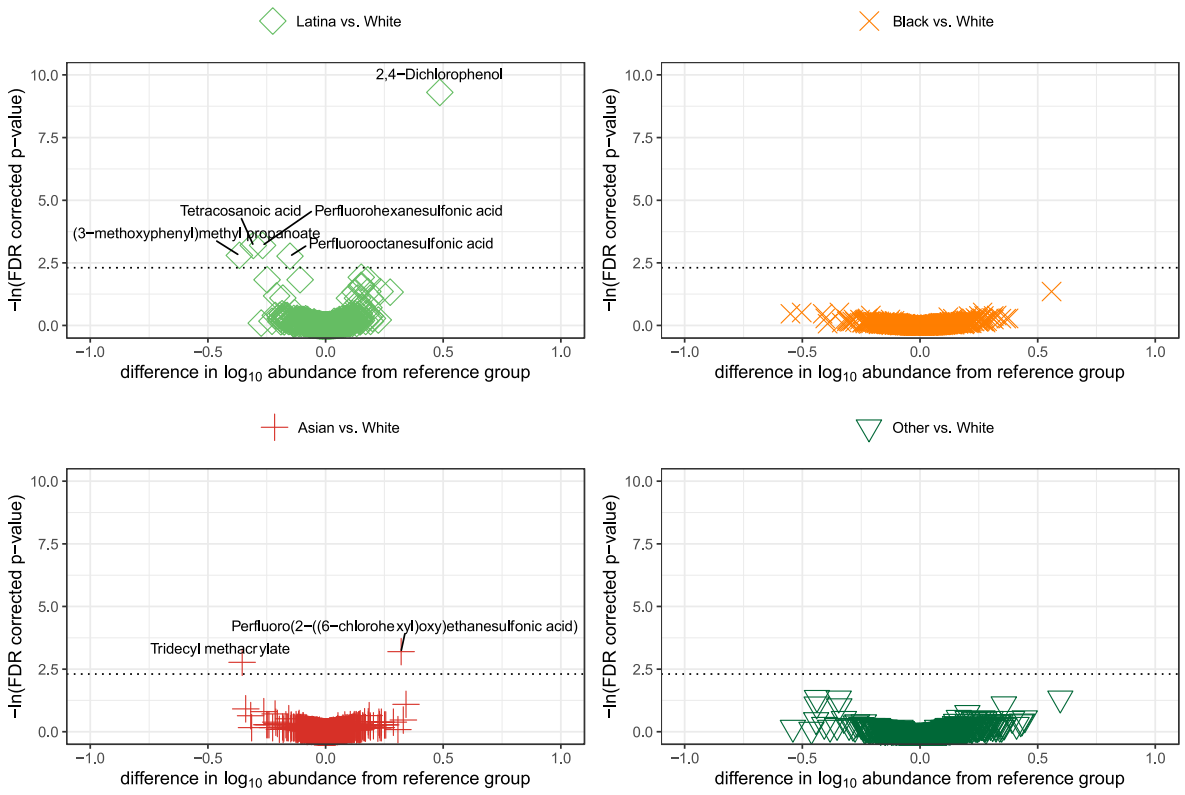

Fig. 3. Abundance differences by race/ethnicity in maternal serum. Note: White participants are the reference group. The dotted line indicates a false discovery rate (FDR) p-value of 0.1. Chemical features with abundance differences significant at the FDR-adjusted level of 0.1 are annotated with their likely names.

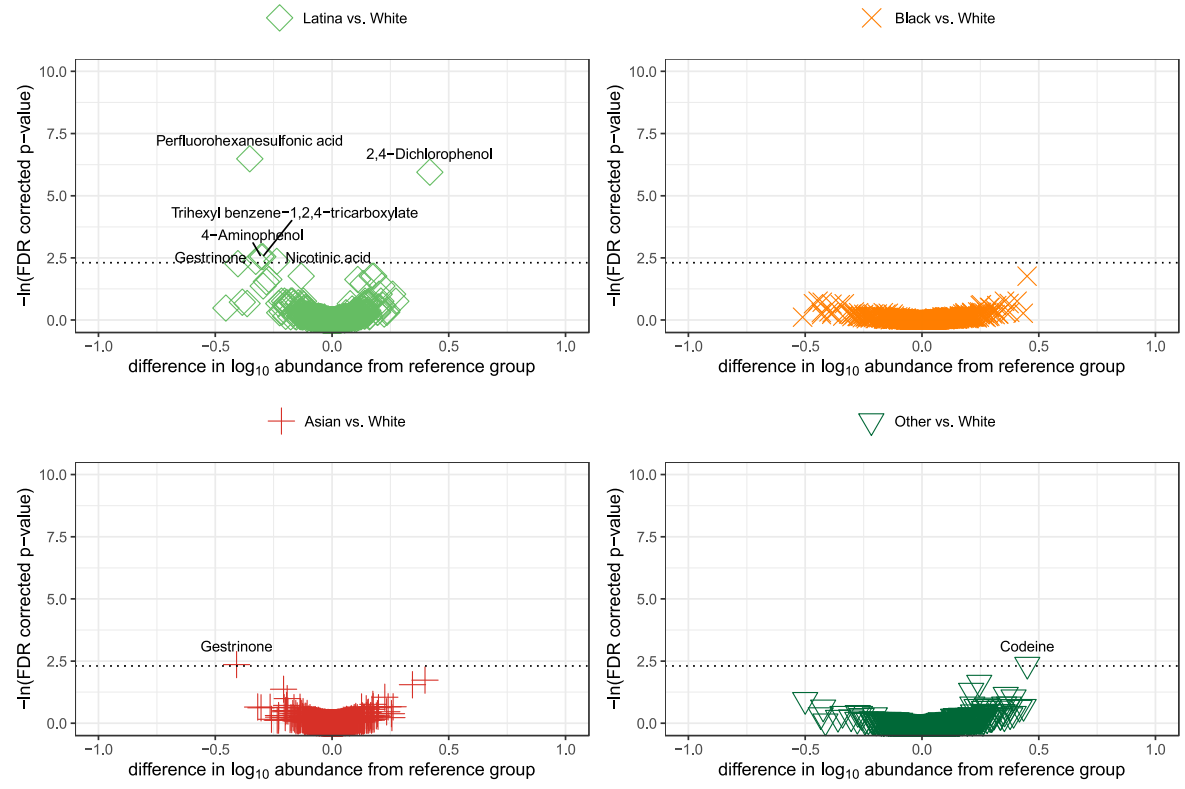

Fig. 4. Abundance differences by race/ethnicity in cord serum. Note: White participants are the reference group. The dotted line indicates a false discovery rate (FDR) p-value of 0.1. Chemical features with abundance differences significant at the FDR-adjusted level of 0.1 are annotated with their likely names.

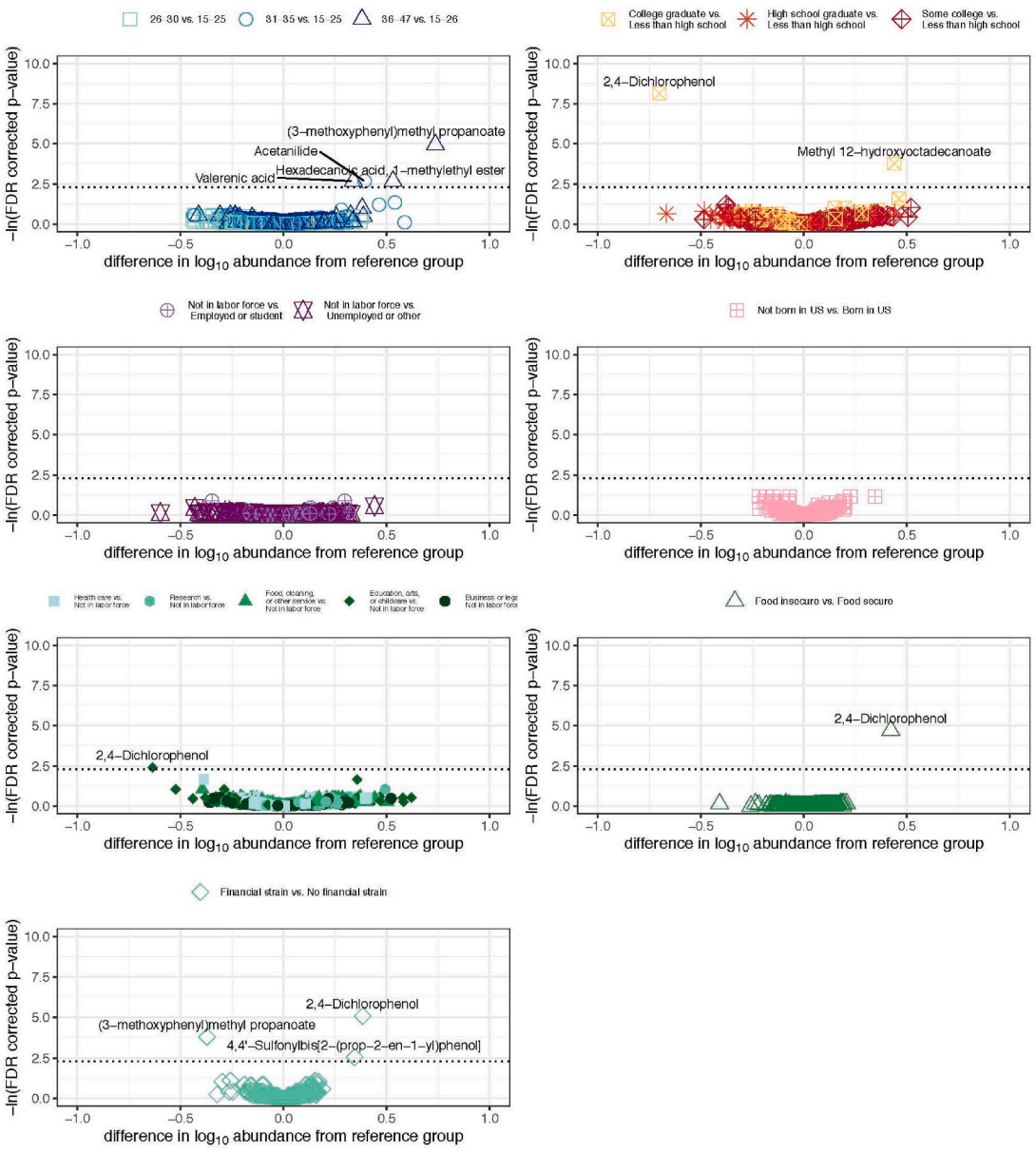

Fig. 5. Abundance differences by in maternal serum by maternal age, educational attainment, employment status, nativity, occupation, food insecurity, and financial strain. Note: The dotted line indicates a false discovery rate (FDR) p-value of 0.1. Chemical features with abundance differences significant at the FDR-adjusted level of 0.1 are annotated with their likely names. Born in the US is the nativity reference group. Food secure is the reference group. No financial strain is the reference group.

ingredient. One chemical feature had lower abundance among those working in education, childcare, or the arts compared to those not in the labor force or unknown occupation and higher abundance among those with food insecurity: 2,4-dichlorophenol. Those with financial strain had higher abundances of a chemical feature annotated as 4,4′-sulfonylbis[2-(prop-2-en-1-yl)phenol], whose source is unknown, and 2,4-dichlorophenol. They also had lower abundances of a chemical feature annotated as (3-methoxyphenyl)methyl propanoate, which is present in pesticides, plastics, and cosmetics.

The patterns in cord serum were slightly different. There were no differences in abundances by maternal age, employment status, or occupation (Fig. 6). By maternal education, one chemical feature had higher abundance in cord blood among college graduates compared to those with less than high school education: perfluorohexanesulfonic acid. The chemical features annotated as 2,4-dichlorophenol (the pesticide ingredient) and ethanol, 2-[2-[2-(2-aminoethoxy)ethoxy] ethoxy]- (whose source is unknown), had lower abundances in cord blood among mothers with a college education. The chemical feature annotated as ethanol, 2-[2-[2-(2-aminoethoxy)ethoxy]ethoxy]- was also lower in abundance among those who had graduated high school compared to those who had less than high school education. The chemical feature annotated as 2,4-dichlorophenol had higher abundances in cord serum among mothers who were food insecure compared to food secure and those who experienced financial strain compared to those who did not. Seven chemical features had differential abundance in cord serum by nativity status: two had higher abundances among those who were not US born and five had higher abundances among those who were US born. The two chemical features with higher abundances among non-US born mothers were annotated as 1-nitronaphthalene, which is present in pharmaceuticals, pesticides, and plastics; and pentyl acetate, which is present in pharmaceuticals, pesticides, plastics, and cosmetics. The five chemical features with higher abundances among US born mothers were annotated as 6-((1-oxoallyl)oxy)hexyl N, N-diethyl-beta-alaninate, which was not present in any of the sources of

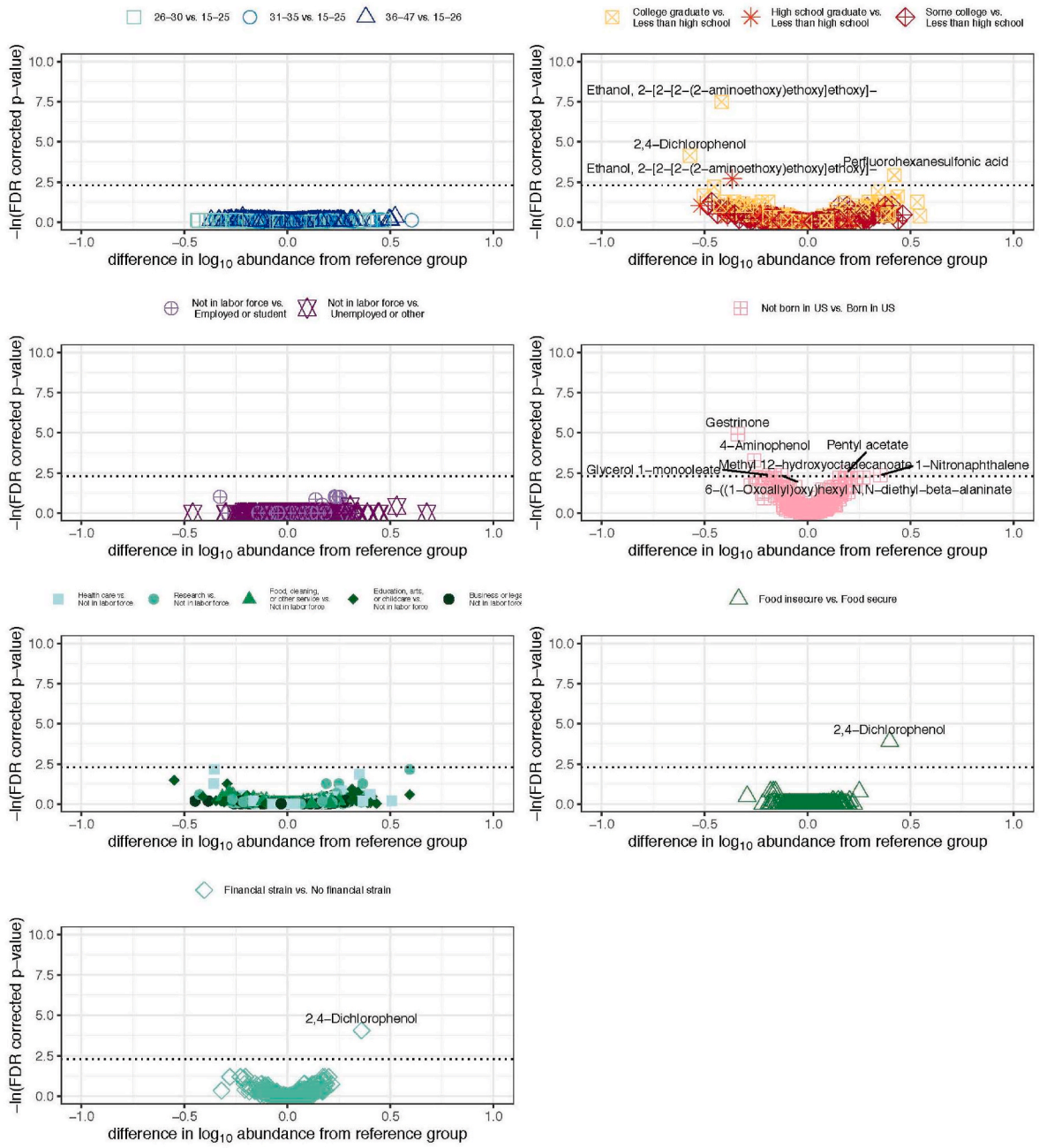

Fig. 6. Abundance differences in cord serum by maternal age, educational attainment, employment status, nativity, occupation, food insecurity, and financial strain. Note: The dotted line indicates a false discovery rate (FDR) p-value of 0.1. Chemical features with abundance differences significant at the FDR-adjusted level of 0.1 are annotated with their likely names. Born in the US is the nativity reference group. Food secure is the reference group. No financial strain is the reference group.

exposure we examined; methyl 12-hydroxyoctadecanoate, which is present in pesticides and cosmetics; gestrinone, which is present in pharmaceuticals and plastics; glycerol 1-monooleate, which is present in pharmaceuticals, pesticides, plastics, and cosmetics; and 4-aminophenol, which is present in pharmaceuticals, pesticides, and cosmetics.

The log-10 abundance differences between sociodemographic or economic groups, the raw and FDR-adjusted p-values, annotations, and likely sources of exposure are available at the first author's github page (https://github.com/degoin/disparities-chemical-exposures-San-Francisco).

4. Discussion

We used nontargeted chemical analysis to evaluate 685 chemical exposures among pregnant women and their newborns in the San Francisco Bay Area. We compared abundances across sociodemographic and economic groups and had several takeaways: women with higher socioeconomic status tended to have higher abundances of PFAS, women with lower socioeconomic status had higher abundances of the chemical feature annotated as 2,4-dichlorophenol, and differences were most apparent when comparing women who delivered at San Francisco General Hospital, a safety net hospital, compared to Mission Bay or Moffit Long hospitals, whose patients tend to have private health insurance.

We hypothesize that the differences we observed between hospitals is due to the differences in the populations they serve. Therefore, stratifying by hospital collapses many sociodemographic and economic factors into one variable, increasing the power to detect differences.

However, to ensure that there were not variations in sample collection across sites that could be responsible for the differences we observed, we tested whether there were differences in the method of delivery and month of sample collection between hospitals and did not find any significant differences. Furthermore, we repeated our analyses comparing abundances between delivery hospitals while controlling for maternal age, educational attainment, race/ethnicity, and nativity, and we found no significant differences in abundances in either maternal or cord blood (Supplemental Figure 3). Furthermore, samples from each hospital were allocated evenly across batches during the analysis stage (Supplemental Figure 4). These factors suggest that the differences we observed between hospitals are likely due to the differences in characteristics of participants between hospitals and not systematic error introduced by our sample collection or analytical methodology. We hypothesize that delivery hospital is a proxy for multiple socioeconomic conditions that differentiate patients who use safety net hospitals versus those that do not, and suggests that cumulative metrics of socioeconomic disadvantage may be more useful in identifying potentially harmful exposures and risk for adverse outcomes. Nevertheless, it is possible that there were differences in the treatment and/or storage protocols at the MB/ML hospitals compared to the ZSFGH that influenced the results. Hospital of delivery was not randomized across batches, so despite conducting batch correction of the abundances, it is possible some batch effects remained that contributed to our findings. It is also possible that differential exposure to pollutants by residential geography plays a role in the differences by hospital that we observed. Participants who delivered at the Mission Bay or Moffit Long hospitals were more likely to live outside the city of San Francisco (Supplemental Figure 5), and lived in Census tracts with lower average Pollution Burden scores from the CalEnviroScreen (35.3 versus 39.6, respectively, p-value <0.01) (Supplemental Figure 6) (August et al., 2021). Given the high cost of living in the Bay Area, where people live is strongly linked to their socioeconomic status. This is consistent with our hypothesis that delivery hospital is a proxy for socioeconomic factors, which may then partially influence place-based exposures to environmental chemicals.

Our most consistent finding was differences in the chemical feature annotated as 2,4-dichlorophenol by socioeconomic status and race/ethnicity. In both maternal and cord serum, there were higher abundances in Latina compared to white women, higher abundances among those who delivered at ZSFGH compared to Mission Bay, higher abundances among those with food insecurity, higher abundances among those with financial strain, and lower abundances among those with a college degree compared to those who had not finished high school. In maternal serum only, we also observed lower abundances among those working in education, childcare, or the arts compared to not in the labor force or unknown occupation. In order to better identify the source of this chemical feature, we conducted some post-hoc analyses using QTOF to get MS2 data. Using MSMS fragmentation information, we determined that the chemical feature was likely either 2,4-dichlorophenol or 2,5-dichlorophenol (Supplemental Figure 7), both isomers of which are used in the pesticide, fertilizer, and other agricultural chemical manufacturing sectors of the economy. 2,5-dichlorophenol is a major metabolite of p-dichlorobenzene, which is a chemical intermediate for dyes, moth repellants, and toilet bowl deodorizers (Yoshida et al., 2002). 2,4-dichlorophenol is an intermediate in the production of herbicides and antihelminthic pesticides (NCfB, 2021), and is the main metabolite of 2,4-dichlorophenoxyacetic acid, a phenoxyalkanoic acid herbicide (Ju et al., 2019). Both 2,4-dichlorophenol and 2,5-dichlorophenol are also byproducts of the chlorination of drinking water and industrial waste water, and previous studies have found elevated levels among groups with lower socioeconomic status (Ye et al., 2014). Toxicological evidence suggests 2,4-dichlorophenol may be a developmental and reproductive toxicant (Aoyama et al., 2005), and epidemiological evidence has shown 2,5-dichlorophenol is associated with lower age of menarche in girls (Buttke et al., 2012) and lower birth weight in boys (Wolff et al., 2008).

Other chemical features that were significantly different across at least one sociodemographic or economic group in both maternal and cord sera were annotated as (3-methoxyphenyl)methyl propanoate (present in pesticides, plasticizers, and cosmetics), methyl 12-hydroxyoctadecanoate (present in pesticides and cosmetics), perfluorohexanesulfonic acid (a PFAS), and tetracosanoic acid (present in pharmaceuticals, plasticizers, and cosmetics) (Supplemental Tables 1 and 2). In maternal serum, we observed higher abundances of (3-methoxyphenyl)methyl propanoate among participants delivering at the MB/ML hospitals compared to ZSFGH, among white compared to Latinas, among older compared to younger participants and among those not experiencing financial strain compared to those experiencing financial strain. In cord serum, we observed higher abundances of 3-methoxyphenyl)methyl propanoate among participants delivering at MB/ML hospitals compared to ZSFGH. We also observed higher abundances of methyl 12-hydroxyoctadecanoate in both maternal and cord sera among participants delivering at MB/ML hospitals compared to ZSFGH. Abundances in maternal serum were also higher among college graduates compared to those with less than high school, and higher in cord serum among those with mothers who were born in the US. white participants had higher abundances of perfluorohexanesulfonic acid in both maternal and cord serum compared to Latina participants. In cord serum, we also observed higher abundances of perfluorohexanesulfonic acid among those who delivered at MB/ML, and higher abundances among those who graduated college. We observed higher abundances of the feature annotated as tetracosanoic acid in both maternal and cord sera among those who delivered at MB/ML, and higher abundances in white participants compared to Latinas in maternal serum only. Overall, women and neonates with higher socioeconomic and social privilege tended to have higher abundances of chemical features annotated as (3-methoxyphenyl)methyl propanoate, methyl 12-hydroxyoctadecanoate, perfluorohexanesulfonic acid, and tetracosanoic acid in their sera.

There were several limitations to our study. While the nontargeted analysis approach allowed us to screen for a larger number of chemicals, we were not able to identify many of the chemical features beyond their chemical formulas. Since these chemicals were not confirmed with analytical standards or matched to MS/MS spectral libraries it is possible the annotations do not indicate the correct structure. While post-hoc MS/MS experiments suggest the chemical feature that was more abundant among the populations experiencing greater social and economic disadvantage was likely either 2,4-dichlorophenol or 2,5-dichlorophenol, we were not able to confirm this with analytical standards. Furthermore, the LC-QTOF/MS instruments used in this study have relatively high detection limits which may have limited our ability to detect chemicals that were present at lower concentrations. Our participants were relatively sociodemographically and economically diverse, although some groups had small numbers which limited our power to detect differences. For instance, the Black and Other race participants in our study had some large differences in abundance levels compared to white participants, but the small sample size meant that these differences were not statistically significant.

Overall, our nontargeted approach allowed us to analyze differences in abundance of 685 chemical features across socioeconomic and demographic groups of pregnant women and their children in San Francisco, California. We found sera of women in lower socioeconomic groups had significantly higher abundances of a chemical feature that was likely either 2,4-dichlorophenol or 2,5-dichlorophenol, both of which have potential endocrine-disrupting effects. We also found higher abundances of PFAS among women in higher socioeconomic status groups. Our analysis indicates that chemical exposures differ across groups in society, especially between women who delivered at the private versus safety net hospitals, likely due to the populations served by each type of hospital. Our nontargeted approach is a great tool for hypothesis generating, and offers a unique opportunity for identifying compounds that can be further evaluated with targeted biomonitoring studies. Ultimately, nontargeted approaches allow us to screen pregnant

women for a higher number of environmental chemical exposures, which may be an important driver of disparities in birth outcomes by socioeconomic status.

Authors' contributions

DEG contributed to the design of the study, and conducted the data analysis, interpreted the data, wrote the manuscript, edited the manuscript. DA contributed to the design of the study, the data analysis, the data interpretation, and edited the manuscript. MW conducted the non-targeted analyses, contributed to the data interpretation, and edited the manuscript. TJ conducted the non-targeted analyses, contributed to the data interpretation, and edited the manuscript. JSP contributed to the design of the study, conducted the non-targeted analysis, contributed to the data interpretation, and edited the manuscript. MS contributed to the design of the study, the data interpretation, and edited the manuscript. RMF contributed to the design of the study, the data interpretation, and edited the manuscript. ED contributed to the design of the study, managed recruitment of participants and acquisition of data, and edited the manuscript. MGZ contributed to the acquisition of the data, data interpretation, and edited the manuscript. TJW designed the study, acquired funding for the study, managed the data acquisition, contributed to the data interpretation and edited the manuscript.

Declarations

4.1. Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Boards of the University of California, San Francisco (IRB number 13–12160).

Availability of data and materials

Data is available on the Metabolomics Workbench. Code and results are available at https://github.com/degoin/disparities-chemical-exposures-San-Francisco.

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Declaration of competing interest

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

Data availability

Data is available on the Metabolomics Workbench. Code and results are available at https://github.com/degoin/disparities-chemical-exposures-San-Francisco

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.114158.

References

Abrahamsson, D., Wang, A., Jiang, T., Wang, M., Siddharth, A., Morello-Frosch, R., et al., 2020. Comprehensive Non-targeted Analysis of the Prenatal Exposome Reveals Significant Differences in Chemical Enrichment between Maternal and Fetal Samples.

Andra, S.S., Austin, C., Patel, D., Dolios, G., Awawda, M., Arora, M., 2017. Trends in the application of high-resolution mass spectrometry for human biomonitoring: an analytical primer to studying the environmental chemical space of the human exposome. Environ. Int. 100, 32–61.

Aoyama, H., Hojo, H., Takahashi, K.L., Shimizu, N., Araki, M., Harigae, M., et al., 2005. A two-generation reproductive toxicity study of 2, 4-dichlorophenol in rats. J. Toxicol. Sci. 30 (Special), S59–S78.

August, L., Bangia, K., Plummer, L., Prasad, S., Ranjbar, K., Slocombe, A., et al., 2021. Update to the California Communities Environmental Health Screening Tool CalEnviroScreen 4.0 Public Review Draft. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment.

Birnbaum, L.S., Fenton, S.E., 2003. Cancer and developmental exposure to endocrine disruptors. Environ. Health Perspect. 111 (4), 389–394.

Buttke, D.E., Sircar, K., Martin, C., 2012. Exposures to endocrine-disrupting chemicals and age of menarche in adolescent girls in NHANES (2003–2008). Environ. Health Perspect. 120 (11), 1613–1618.

Egeghy, P.P., Judson, R., Gangwal, S., Mosher, S., Smith, D., Vail, J., et al., 2012. The exposure data landscape for manufactured chemicals. Sci. Total Environ. 414, 159–166.

Ejaredar, M., Nyanza, E.C., Ten Eycke, K., Dewey, D., 2015. Phthalate exposure and childrens neurodevelopment: a systematic review. Environ. Res. 142, 51–60.

Gutiérrez-Torres, D.S., Barraza-Villarreal, A., Hernandez-Cadena, L., Escamilla-Nuñez, C., Romieu, I., 2018. Prenatal exposure to endocrine disruptors and Cardiometabolic risk in preschoolers: a systematic review based on cohort studies. Annals of global health 84 (2), 239.

Halldorsson, T.I., Rytter, D., Haug, L.S., Bech, B.H., Danielsen, I., Becher, G., et al., 2012. Prenatal exposure to perfluorooctanoate and risk of overweight at 20 years of age: a prospective cohort study. Environ. Health Perspect. 120 (5), 668–673.

Jiang, T., Wang, M., Wang, A., Abrahamsson, D., Kuang, W., Morello-Frosch, R., et al., 2021. Large-scale implementation and flaw investigation of human serum suspect screening analysis for industrial chemicals. J. Am. Soc. Mass Spectrom. 32 (9), 2425–2435.

Ju, Z., Liu, S.-S., Xu, Y.-Q., Li, K., 2019. Combined toxicity of 2, 4-dichlorophenoxyacetic acid and its metabolites 2, 4-dichlorophenol (2, 4-DCP) on two nontarget organisms. ACS Omega 4 (1), 1669–1677.

Lam, J., Lanphear, B.P., Bellinger, D., Axelrad, D.A., McPartland, J., Sutton, P., et al., 2017. Developmental PBDE exposure and IQ/ADHD in childhood: a systematic review and meta-analysis. Environ. Health Perspect. 125 (8), 086001.

Liu, Z., Cai, L., Liu, Y., Chen, W., Wang, Q., 2019. Association between prenatal cadmium exposure and cognitive development of offspring: a systematic review. Environ. Pollut. 254, 113081.

Mendez, M.A., Garcia-Esteban, R., Guxens, M., Vrijheid, M., Kogevinas, M., Goñi, F., et al., 2011. Prenatal organochlorine compound exposure, rapid weight gain, and overweight in infancy. Environ. Health Perspect. 119 (2), 272–278.

NCfB, Information, 2021. PubChem Annotation Record for 2,4-DICHLOROPHENOL.

Panagopoulos Abrahamsson, D., Wang, A., Jiang, T., Wang, M., Siddharth, A., Morello-Frosch, R., et al., 2021. A comprehensive non-targeted analysis study of the prenatal exposome. Environ. Sci. Technol. 55 (15), 10542–10557.

Perera, F., Herbstman, J., 2011. Prenatal environmental exposures, epigenetics, and disease. Reprod. Toxicol. 31 (3), 363–373.

Plassmann, M.M., Fischer, S., Benskin, J.P., 2018. Nontarget time trend screening in human blood. Environ. Sci. Technol. Lett. 5 (6), 335–340.

Rochester, J.R., Bolden, A.L., Kwiatkowski, C.F., 2018. Prenatal exposure to bisphenol A and hyperactivity in children: a systematic review and meta-analysis. Environ. Int. 114, 343–356.

Sapbamrer, R., Hongsibsong, S., 2019. Effects of prenatal and postnatal exposure to organophosphate pesticides on child neurodevelopment in different age groups: a systematic review. Environ. Sci. Pollut. Control Ser. 26 (18), 18267–18290.

Sobus, J.R., DeWoskin, R.S., Tan, Y.-M., Pleil, J.D., Phillips, M.B., George, B.J., et al., 2015. Uses of NHANES biomarker data for chemical risk assessment: trends, challenges, and opportunities. Environ. Health Perspect. 123 (10), 919–927.

Sobus, J.R., Wambaugh, J.F., Isaacs, K.K., Williams, A.J., McEachran, A.D., Richard, A. M., et al., 2018. Integrating tools for non-targeted analysis research and chemical safety evaluations at the US EPA. J. Expo. Sci. Environ. Epidemiol. 28 (5), 411–426.

Terry, M.B., Michels, K.B., Brody, J.G., Byrne, C., Chen, S., Jerry, D.J., et al., 2019. Environmental exposures during windows of susceptibility for breast cancer: a framework for prevention research. Breast Cancer Res. 21 (1), 1–16.

Valvi, D., Casas, M., Mendez, M.A., Ballesteros-Gómez, A., Luque, N., Rubio, S., et al., 2013. Prenatal bisphenol a urine concentrations and early rapid growth and overweight risk in the offspring. Epidemiology 791–799.

Wang, A., Abrahamsson, D.P., Jiang, T., Wang, M., Morello-Frosch, R., Park, J.-S., et al., 2021. Suspect screening, prioritization, and confirmation of environmental

chemicals in maternal-newborn pairs from San Francisco. Environ. Sci. Technol. 55 (8), 5037–5049.
Williams, A.J., Grulke, C.M., Edwards, J., McEachran, A.D., Mansouri, K., Baker, N.C., et al., 2017. The CompTox Chemistry Dashboard: a community data resource for environmental chemistry. J. Cheminf. 9 (1), 1–27.
Wolff, M.S., Engel, S.M., Berkowitz, G.S., Ye, X., Silva, M.J., Zhu, C., et al., 2008. Prenatal phenol and phthalate exposures and birth outcomes. Environ. Health Perspect. 116 (8), 1092–1097.
Ye, X., Wong, L.-Y., Zhou, X., Calafat, A.M., 2014. Urinary concentrations of 2, 4-dichlorophenol and 2, 5-dichlorophenol in the US population (national health and nutrition examination survey, 2003–2010): trends and predictors. Environ. Health Perspect. 122 (4), 351–355.
Yoshida, T., Andoh, K., Fukuhara, M., 2002. Urinary 2, 5-dichlorophenol as biological index for p-dichlorobenzene exposure in the general population. Arch. Environ. Contam. Toxicol. 43 (4), 481–485.
Zarean, M., Poursafa, P., Amin, M.M., Kelishadi, R., 2018. Association of endocrine disrupting chemicals, bisphenol A and phthalates, with childhood obesity: a systematic review. Journal of Pediatrics Review 6 (1), 20–35.