Metabolomics (2024) 20:6
https://doi.org/10.1007/s11306-023-02074-y

ORIGINAL ARTICLE

Maternal and newborn metabolomic changes associated with urinary polycyclic aromatic hydrocarbon metabolite concentrations at delivery: an untargeted approach

Jagadeesh Puvvula[1] · Kathrine E. Manz[2] · Joseph M. Braun[3] · Kurt D. Pennell[2] · Emily A. DeFranco[4] · Shuk-Mei Ho[5] · Yuet-Kin Leung[5] · Shouxiong Huang[6] · Ann M. Vuong[7] · Stephani S. Kim[8] · Zana P. Percy[6] · Priyanka Bhashyam[9] · Raymund Lee[9] · Dean P. Jones[10] · Vilinh Tran[10] · Dasom V. Kim[11] · Aimin Chen[1]

Received: 7 August 2023 / Accepted: 28 November 2023 / Published online: 14 December 2023

Abstract

Introduction Prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) has been associated with adverse human health outcomes. To explore the plausible associations between maternal PAH exposure and maternal/newborn metabolomic outcomes, we conducted a cross-sectional study among 75 pregnant people from Cincinnati, Ohio.

Method We quantified 8 monohydroxylated PAH metabolites in maternal urine samples collected at delivery. We then used an untargeted high-resolution mass spectrometry approach to examine alterations in the maternal (n = 72) and newborn (n = 63) serum metabolome associated with PAH metabolites. Associations between individual maternal urinary PAH metabolites and maternal/newborn metabolome were assessed using linear regression adjusted for maternal and newborn factors while accounting for multiple testing with the Benjamini-Hochberg method. We then conducted functional analysis to identify potential biological pathways.

Results Our results from the metabolome-wide associations (MWAS) indicated that an average of 1% newborn metabolome features and 2% maternal metabolome features were associated with maternal urinary PAH metabolites. Individual PAH metabolite concentrations in maternal urine were associated with maternal/newborn metabolome related to metabolism of vitamins, amino acids, fatty acids, lipids, carbohydrates, nucleotides, energy, xenobiotics, glycan, and organic compounds.

Conclusion In this cross-sectional study, we identified associations between urinary PAH concentrations during late pregnancy and metabolic features associated with several metabolic pathways among pregnant women and newborns. Further studies are needed to explore the mediating role of the metabolome in the relationship between PAHs and adverse pregnancy outcomes.

Keywords Polycyclic aromatic hydrocarbons · Pregnancy · Fetus · Metabolome · Untargeted metabolomics

1 Introduction

Polycyclic aromatic hydrocarbons (PAHs) are lipophilic compounds that exist as multiple congeners with at least two benzo rings fused together in linear or angular configurations (Henkler et al., 2012). Environmental exposure to PAHs among humans occurs primarily via inhalation of air pollutants from vehicle exhaust, tobacco smoke, biomass (agricultural residual, prescribed, residential firewood) burning, wildfires as well as ingestion of smoked/barbecued meat, dairy products, and contaminated water (Amirdivani et al., 2019; US-EPA, 1983). Among PAHs, exposure to anthracene and naphthalene could be from interaction with consumer products such as dyes, synthetic fiber, plastics, insecticides, and moth repellents (Harrison, 2021). PAHs are short-lived chemicals, with a median half-life ranging from 2.9 to 6.1 h upon oral exposure and 9.8 h via respiratory exposure in humans (Brzeźnicki et al., 1997; Li et al., 2012). Within the spectrum of PAH metabolites, 3-hydroxyfluorene and 1-hydroxyphenanthrene had up to 84% longer elimination half-lives (6.1 and 5.1 h, respectively) compared to 2-napthol with a median half-life of 2.5 h (Li et al., 2012). Among the 10 urinary PAHs measured by Li et

Extended author information available on the last page of the article

al., 1-/2-naphthol (66.3 and 64.4 µg/g creatinine) had higher gastrointestinal uptake upon ingestion of barbecued food (Li et al., 2012).

At the cellular level, PAHs bind to the aryl hydrocarbon receptors (AhR), which will disrupt the chaperone complex and translocate AhR to the nucleus (Låg et al., 2020). This may lead to the formation of heterodimers [aryl hydrocarbon receptor nuclear translocator (ARNT)] that bind to xenobiotic response elements and induce the expression of several genes in the biotransformation pathway. During the phase-II metabolism of PAHs, epoxide hydrolases convert them into PAH-epoxides, increasing their hydrophilicity for excretion, but this increases the protein/nucleic acid binding capacity that disrupts cellular function (Miller & Ramos, 2001). Additionally, AhR-ARNT complex induces the expression of cytochrome P450 enzymes: 1A1, 1A2, 1B1; glutathione S-transferase (GST-1); UDP-glucuronosyltransferases (UGT1A1, UGT1A6); NADPH-dependent quinone oxidoreductase NQO1; and aldehyde dehydrogenase (ALDH3A1) (Sansen et al., 2007; Stejskalova et al., 2011). These enzymes are involved in cell cycle regulation, immune function and metabolism and transportation of exo-/endogenous compounds (Sansen et al., 2007; Stejskalova et al., 2011).

Pregnancy is a period of susceptibility to PAH exposures that may result in adverse pregnancy or birth outcomes. Exposure to PAHs during pregnancy has shown positive associations with placental corticotropin-releasing hormone and fetal/maternal PAH-DNA adduct ratio (Jedrychowski et al., 2013). PAH metabolites have also been associated with lower child height, a higher prevalence of asthma among female children and increased symptoms of anxiety/depression and attention problems (Barrett et al., 2022; Jedrychowski et al., 2013, 2015; Loftus et al., 2022; Perera et al., 2012; Wang et al., 2008). In addition, endothelial cell line studies demonstrated that ARNT overexpression is negatively associated with placental angiogenesis, organogenesis, and lipid metabolism (Ji et al., 2019; Su et al., 2015; Yim et al., 2006).

While evidence from human and cell line studies supports the association between PAH exposure and adverse biological outcomes, there is a literature gap regarding the potential mechanistic association between prenatal PAH exposures and fetal health. Metabolome-wide association studies (MWAS) have the potential to uncover the biological underpinnings of PAH exposure. These may include disruption of exo-/endogenous metabolites and their association with biological pathways upon exposure to PAHs (Gao et al., 2018). In this regard, Suter et al., assessed metabolome wide associations with PAH exposures using placental tissue in the context of Superfund sites in Harris County, Texas, which revealed alterations in endogenous metabolic pathways (pentose phosphate, inositol phosphate, starch, and sucrose) among pre-term newborns living near a superfund site (Suter et al., 2019). Similar studies conducted among healthy subjects identified associations between PAH exposure and disruption in amino acid, purine, lipid, glucuronic acid, and steroid hormone metabolism, which trigger oxidative stress-related outcomes among humans (Lu et al., 2021; Wang et al., 2015).

Although there is evidence linking PAH exposure to oxidative stress through metabolic disruption, the specific impact of PAH exposure on the metabolome of pregnant women and newborns remains largely unknown. This study aims to provide preliminary data to fill this research gap by examining the associations between maternal urinary PAH metabolite concentrations and metabolic outcomes in both pregnant individuals and their fetuses using untargeted metabolomics. Furthermore, it will investigate potential disruptions in metabolic pathways related to PAH exposure.

2 Methods

2.1 Study participants and sample collection

For this pilot study, we recruited 75 pregnant women between August 2014 and September 2017 from a labor and delivery unit in Cincinnati, Ohio. The study protocol was approved by the University of Cincinnati Institutional Review Board. Study participants were women with singleton pregnancies, between the ages of 18–45 years who presented for delivery at the University of Cincinnati Medical Center and provided written consent for study participation. Subjects with a history of diabetes, thyroid, cardiovascular, renal, hepatic conditions, cancers that affect pregnancy, or severe maternal or fetal complications at the time of enrollment were excluded from this study. During the hospital visit for delivery, we collected 30 mL of maternal urine and 15 mL of maternal venous blood. Additionally, 10mL of cord blood was collected at the time of delivery. Maternal and infant demographic, medical, and pregnancy outcome data were obtained from a questionnaire and medical record review.

2.2 PAH concentrations

The urinary concentrations of eight PAH metabolites (1-Hydroxynaphthalene, 2-Hydroxynaphthalene, 2-Hydroxyfluorene, 1-Hydroxyphenanthrene, 2,3-Hydroxyphenanthrene, 4-Hydroxyphenanthrene, 9-Hydroxyphenanthrene, and 1-Hydroxypyrene) were measured among 75 subjects at NSF International – Applied Research Center in Ann Arbor, MI. Urinary concentrations of these

monohydroxylated PAHs were quantified using ultra-high-performance liquid chromatography coupled with a mass spectrometer (UHPLC-MS-MS) (Onyemauwa et al., 2009). The assays were implemented using a Thermo Scientific Transcend TXII Turbulent Flow system coupled with Thermo Scientific Vantage triple quadrupole mass spectrometer using negative electrospray ionization and multiple reaction monitoring with limit of detection (LOD) for each compound in Table 1.

Each batch contained five calibration standards with $R^2 \geq 0.98$, and duplicate QC samples with three known concentrations. The PAH metabolite concentrations were corrected for possible contaminants using a laboratory blank. The batch run was validated if at least 67% (4 of 6) of total QC samples within ±2 standard deviations within the QC level determined from the historic data for each target analyte. Each sample was extracted using 4-methylumbelliferyl sulfate, 4-methylumbelliferyl glucuronide, and 13C4-4-methylumbelliferone, as the deconjugation standards to monitor the extent of the enzymatic reaction. The metabolite concentration of 2-hydroxyphenanthrene and 3-hydroxyphenanthrene were combined and represented as 2,3-hydroxyphenanthrene. As the proportion of the subjects with urinary PAH metabolite concentrations below LOD is relatively small (≤12%), we used fill-in method to replace values < LOD with LOD divided by the square root of two (Lubin et al., 2004). A composite variable representing low molecular weight (LMWT) PAHs (sigma-LMWT-PAHs) was created using the numeric sum of 7 of 8 PAH metabolites (excludes 1-hydroxypyrene) measured in this study (Alshaarawy et al., 2013; Kim et al., 2021). Additionally, urine creatinine was quantified using an enzymatic method with a LOD of 1.0 mg/dL urine (CDC, 2019). The PAH metabolite concentrations were standardized for urine creatinine to yield concentrations as ng/g creatinine.

Table 1 Summary statistics of PAH metabolite concentrations in maternal urine at delivery, Cincinnati, Ohio (n = 72)

PAH metabolites	LOD*	% < LOD	Median (IQR)**	Median (IQR) – NHANES***
1-Hydroxynaphthalene	0.05	4.0	142.1 (74.5-303.3)	1813.3 (823.8-6376.3)
2-Hydroxynaphthalene	0.05	0.0	4380.7 (2490.5-8461.6)	4245.6 (2120.0-9273.7)
2-Hydroxyfluorene	0.01	1.3	123.9 (73.4-232.7)	194.5 (116.2–460.0)
1-Hydroxyphenanthrene	0.01	0.0	121.9 (74.7-194.4)	126.2 (80.4-207.5)
2,3-Hydroxyphenanthrene	0.02	0.0	101.2 (68.9-154.4)	138.3 (88.4-238.2)
4-Hydroxyphenanthrene	0.01	12.0	14.3 (4.2–20.4)	NA
9-Hydroxyphenanthrene	0.01	8.0	17.7 (10.4–33.3)	NA
1-hydroxypyrene	0.01	1.3	120.3 (70.9–173.0)	105.9 (61.2-197.4)

*ng/L; **ng/g creatinine; IQR-Inter quartile range; ***PAH metabolite concentrations (ng/g creatinine) from the National Health and Nutrition Examination Survey (2003–2016) were obtained from Lu & Ni, 2023

2.3 High-resolution metabolomics

We isolated serum from maternal (n = 72) and cord (n = 63) whole blood samples. Stored frozen serum samples (-80 °C) were thawed on ice to obtain 65 µL of the serum sample for metabolome assays. We then added 130 µL of acetonitrile which contain a mixture of stable isotope standards to the serum sample. Then, the samples were vortex mixed, equilibrated for 30 min, and centrifuged. Metabolomic profiling of the serum samples (10 µL aliquots) was conducted using the Dionex UltiMate 3000 Ultra-High-Performance Liquid Chromatography (UHPLC) coupled with Q-Exactive High-Field (HF) mass spectrometer (Thermo Scientific). We used formic acid, acetonitrile, and UHPLC-MS grade water as the mobile phase for metabolite separation (Walker et al., 2019). The samples were analyzed in triplicate, using a hydrophilic interaction liquid chromatographic (HILIC) column with positive electrospray ionization (ESI) and a C-18 column with negative ESI (Walker et al., 2019; Yu et al., 2013).

The mass spectrometer was operated in full scan mode at 120,000 resolution over a mass-to-charge (m/z) ratio between 85 and 1,275. The raw data files from the mass spectrometer were then processed using the apLCMS R package to generate m/z ratio, retention time, and feature intensity (Yu et al., 2009). Potential batch (n = 4) errors among these metabolic features were corrected using the ComBat algorithm (Johnson et al., 2007). Triplicate injections were summarized using the median value using the xMSanalyzer algorithm (Uppal et al., 2017). We then excluded any metabolite features (m/z & retention time combinations) with ≥20% non-detects among the study subjects. We retained 6,857 features in the negative mode and 10,207 features in the positive mode. The metabolome feature intensities were log10 transformed and standardized to the Z-score scale (unit scaling).

2.4 Data analysis

2.4.1 Metabolome-wide associations (MWAS)

Among the 75 mother-infant pairs included in this study, MWAS with PAHs were evaluated for 72 samples from maternal serum and 63 from cord serum (hereafter referred to as newborn sample) due to the availability of metabolome data. These associations (PAH-MWAS) were evaluated using a linear regression model, considering the intensity of each metabolome feature as the outcome, and each PAH urinary metabolite concentration (urine creatinine adjusted and log-10 transformed) as exposure. Effect estimates were adjusted for maternal BMI, age, tobacco use, education, race and for newborn metabolome-wide associations, we additionally adjusted for maternal parity and newborn's sex, for newborn analysis. In the regression model, we considered maternal BMI, parity, and maternal age on a continuous scale. Whereas tobacco use during pregnancy (yes or no), education (less than a bachelor's degree or with a bachelor's degree/above), race (Non-Hispanic White or Other), and newborn sex (male or female) were considered factors. A total of 17,064 metabolome features from the positive (10,207 features) and negative (6,857 features) modes were combined to assess the metabolome-wide associations with urinary PAH metabolite concentrations. The rate of false positives (Type-I errors) was allowed for up to 20% by using a threshold value from the Benjamini-Hochberg (FDR-BH) procedure (Benjamini & Hochberg, 1995).

2.4.2 Pathway analysis

We considered LC-MS mixed mode (combining features from positive and negative mode) and up to 30 potential adducts for the metabolome features (S1). The m/z, retention time, LC-MS mode, and p-value corresponding to each metabolome feature, were extracted from each PAH-MWAS results to identify statistically significant alterations in metabolic pathways. The pathway analysis was conducted in 18 batches in a combination of each urinary PAH metabolite and participant group (maternal or newborn), using the mummichog version 2.0 algorithm available through the MetaboAnalystR R package (Li et al., 2013; Pang et al., 2021).

Pathway analysis was performed using a mass tolerance of up to 5 ppm, including all the metabolome features to estimate the background, and the FDR-BH thresholds were inputted as the p-value cutoff (S2). Peak set enrichment analysis (hereafter referred to as pathway analysis) was conducted using the current version of Homo Sapiens – MFN pathway library. We then extracted the pathway names, total metabolites in the pathway, total hits, expected hits, significant hits, and the Fisher-exact test results corresponding to each pathway. Pathways with a statistically significant number of hits per pathway from the pathway analysis were identified using the one-tailed Fisher Exact test ($p < 0.05$) following Gaussian hypergeometric probability distribution (Li et al., 2013; Pang et al., 2021). Additionally, we calculated the enrichment factor by dividing significant hits with expected hits per pathway.

2.4.3 Sensitivity analysis

As identification of pathways that are significantly altered due to exposures could be misrepresented based on the pathway analysis parameters, we conducted sensitivity analysis to explore uncertainty (Wieder et al., 2021, 2022). To minimize the uncertainty in the pathway analysis, we performed the analysis using three p-value thresholds (0.05, 0.1, and 0.5) that are commonly used as thresholds in pathway analysis. Pathway enrichment analysis with p-values ≤ 0.01 led to convergence issues. We then reported the pathways that overlap using 3 p-value thresholds along with the FDR-BH threshold.

The analysis was conducted using R version 4.2.2 and R library tidyverse version 2.0 (R-Core-Team, 2022; Wickham et al., 2019).

3 Results

This study included pregnant women with a median age of 29 years (IQR 24.8–32.0) at the time of delivery, most (83.3%) were parous, and the majority (68%) lived in the same residence throughout their pregnancy period. Nearly half of the participants were non-Hispanic Black women (47.2%); the median BMI of mothers was 25.9 kg/m^2 (IQR 22.5–30.5) and 17% of the women smoked during their pregnancy. Among the maternal study participants, 75% of women attained less than a 4-year college education, 64% with a household income less than the median household income for Cincinnati, OH. All the mothers enrolled in this study delivered a newborn at full-term, with a gestational age range from 37 to 41 weeks. Among the newborns, 58.3% are male (S3). Three of the eight PAH metabolites (2-Hydroxynaphthalene, 1-Hydroxyphenanthrene, and 2,3-Hydroxyphenanthrene) quantified from the maternal urine samples in this study were detected among all the study subjects (Table 1).

Over 1% (1.3%, 219/17,064) of newborn and 2% (334/17,064) of maternal metabolome features were associated (p-value below the FDR thresholds listed in S2) with each of the maternal urinary PAH metabolite concentrations. Most (79%, 3,105/3,944) of the newborn's metabolome

features are positively associated with at least one PAH metabolite concentration measured in maternal urine. A similar trend was observed with the maternal MWAS, 53% (3,200 of 6,020) of the features associated with any of the maternal urinary PAH metabolite concentrations were towards the positive direction. Metabolome features in newborns associated with maternal PAH metabolites were dominated (30%; 1,157/3,944) by the maternal urinary concentration of 1-hydroxynaphthalene. Among pregnant women, MWAS were dominated by (40%, 2,399/6,020) 9-hydroxyphenanthrene (Table 2; Fig. 1).

In pathway analysis, we observed 59 unique pathways (newborns = 25; women = 50; overlap = 16) significantly (Fisher-Exact p-value < 0.05) associated with maternal PAH metabolite concentrations (S4). Notably, among these pathways overlapped in both maternal and newborn, 14 of 16 primarily involve amino acid metabolism. The maternal urinary PAH metabolite, 1-hydroxyphenanthrene, showed consistent associations with enriched pathways; these pathways include arginine and proline, ascorbate, aldarate, urea cycle/amino group, and lysine metabolism across both maternal and newborn metabolomes. Furthermore, the PAH metabolite, 1-hydroxynaphthalene, was commonly associated with bile acid biosynthesis in pathway analysis of maternal and newborn metabolome.

Table 2 Metabolic features associated with maternal urinary PAH metabolite concentrations

PAH metabolites	Newborn		Maternal	
	β (-)	β (+)	β (-)	β (+)
1-Hydroxynaphthalene	226 (1.56)	931 (5.46)	41 (0.24)	120 (0.70)
2-Hydroxynaphthalene	149 (0.87)	265 (1.55)	173 (1.01)	235 (1.38)
2-Hydroxyfluorene	38 (0.22)	335 (1.96)	43 (0.25)	228 (1.34)
1-Hydroxyphenanthrene	65 (0.38)	229 (1.34)	825 (4.83)	737 (4.32)
2,3-Hydroxyphenanthrene	51 (0.30)	202 (1.18)	144 (0.84)	216 (1.27)
4-Hydroxyphenanthrene	74 (0.43)	324 (1.90)	84 (0.49)	182 (1.07)
9-Hydroxyphenanthrene	51 (0.30)	172 (1.01)	1,345 (7.88)	1,054 (6.18)
∑ LMWT-PAHs	49 (0.29)	187 (1.10)	109 (0.64)	181 (1.06)
1-Hydroxypyrene	136 (0.80)	460 (2.70)	56 (0.33)	247 (1.45)

Association between maternal urine PAH metabolite concentrations and the intensity of metabolome features (17,064 features) estimated using linear regression with an FDR threshold of up to 20%. The numeric values represent the frequency and percent [n(%)] of metabolome features that are significantly (p-value < 20% FDR-BH threshold) associated with maternal urinary PAH metabolite concentrations. Beta with either a positive or negative sign represent the direction of beta coefficients

Among these PAH metabolite associations in newborns, 1-hydroxyphenanthrene contributed to the highest number of associations in pathway analysis, where there are only two pathways that were altered exclusively by the 1-hydroxyphenanthrene and nine pathways that were altered by at least another PAH metabolite. In contrast, 1-hydroxypyrene exclusively contributed to the alteration of 3 pathways in newborns (S5). The pregnant women had a greater impact in terms of number of altered pathway pathways, with up to 27 pathways significantly altered due to the 9-hydroxyphenanthrene (S6). Among the 27 pathways altered by 9-hydroxyphenanthrene, 17 are exclusive and 9 pathways were altered by 9-hydroxyphenanthrene and 1-hydroxyphenanthrene.

Across the range of pathways associated with the PAH-metabolome in this study, we observed that metabolism of vitamins, amino acids, and organic compounds were associated with PAH metabolite concentrations. In both newborns and pregnant women, the amino acid metabolism pathways that are associated with maternal PAH metabolites exhibited a relatively lower enrichment factor. Whereas the lipid (arachidonic acid), fatty acid, xenobiotic and carbohydrate metabolism pathways yielded a relatively higher enrichment factor among the pregnant women. Additionally, lipid (sphingolipid, bile acid), vitamin (cholecalciferol) metabolism pathways are with a higher enrichment factor among the newborns (Fig. 2).

In newborns, five of eight PAH metabolites (2-hydroxynaphthalene, 2-hydroxyfluorene, 1-hydroxyphenanthrene, 2,3-hydroxyphenanthrene, and 1-hydroxypyrene) were associated with amino acid (alanine and aspartate) metabolism. In contrast, 6 PAH metabolites were associated with maternal leukotriene metabolism. Notably, PAH metabolites were associated with the putative anti-inflammatory metabolite formation, prostaglandin formation and R group synthesis in pregnant women are with a relatively higher enrichment factor (Fig. 2). Additionally, we observed associations with xenobiotics biodegradation/metabolism pathway that is known to be directly related to PAH metabolites.

In the maternal metabolome enrichment analysis, a similar number of pathways altered due to the PAH metabolites while using different p-values as cutoff (S7). However, while analyzing the fetal metabolome, we observed variance in enriched pathway counts by p-value thresholds: the lowest number of pathways (25) under the FDR-BH threshold and the highest number of pathways while using p < 0.05 as the cutoff (S7). In our enrichment analysis of both the maternal and newborn metabolome, we observed congruence in enriched pathways while using p-value cutoffs up to 0.1 (S8). Yet, in the pathway analysis utilizing a p-value threshold of < 0.5, distinct pathways emerged compared to the three cutoff values considered in this study.

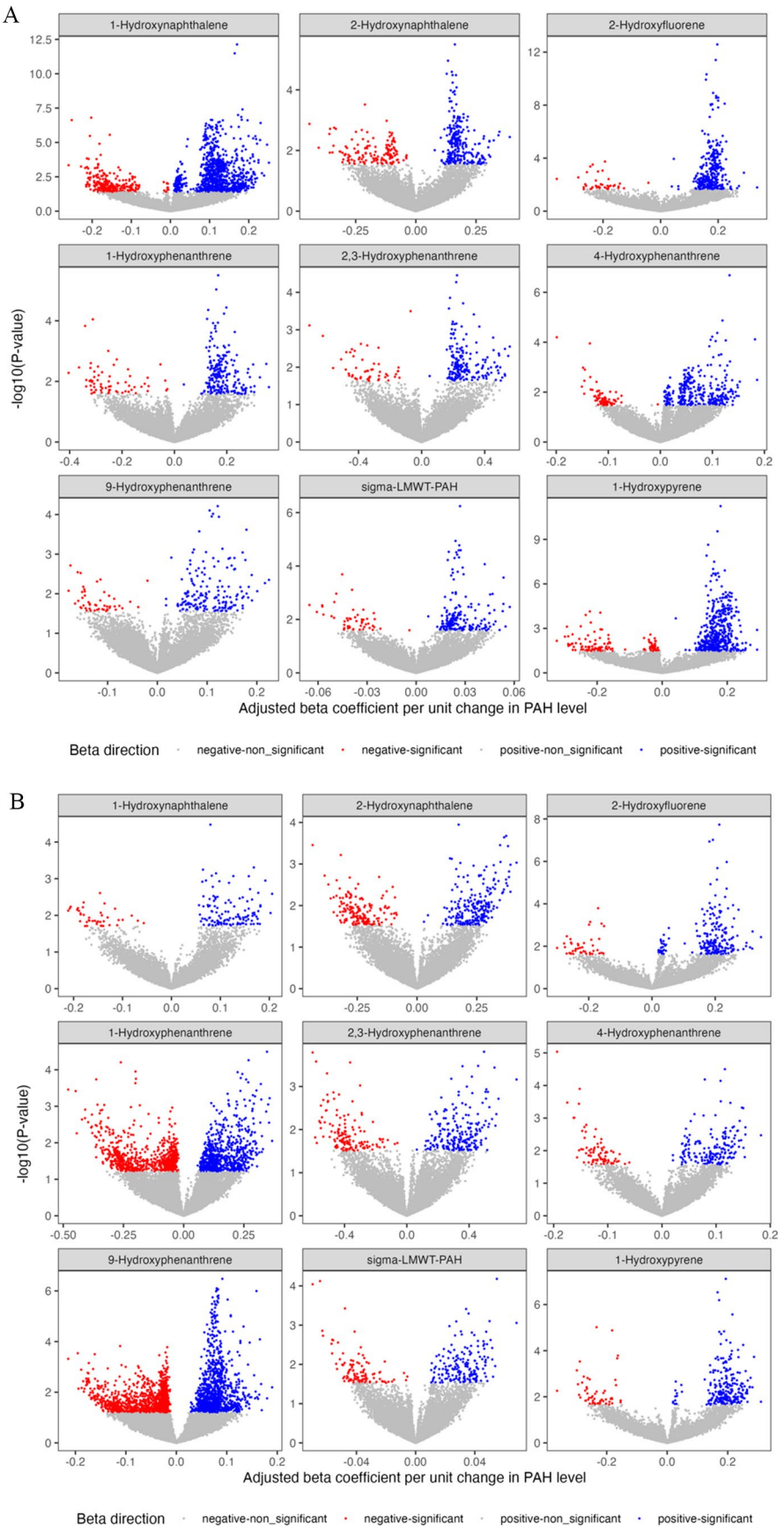

Fig. 1 PAH metabolite – Metabolome wide associations. **A**. Newborn and **B**. maternal. X-axis represent the adjust effect estimates and y-axis represent p-value on log-10 scale. Red color denotes negative significant associations; blue color represents positive significant associations

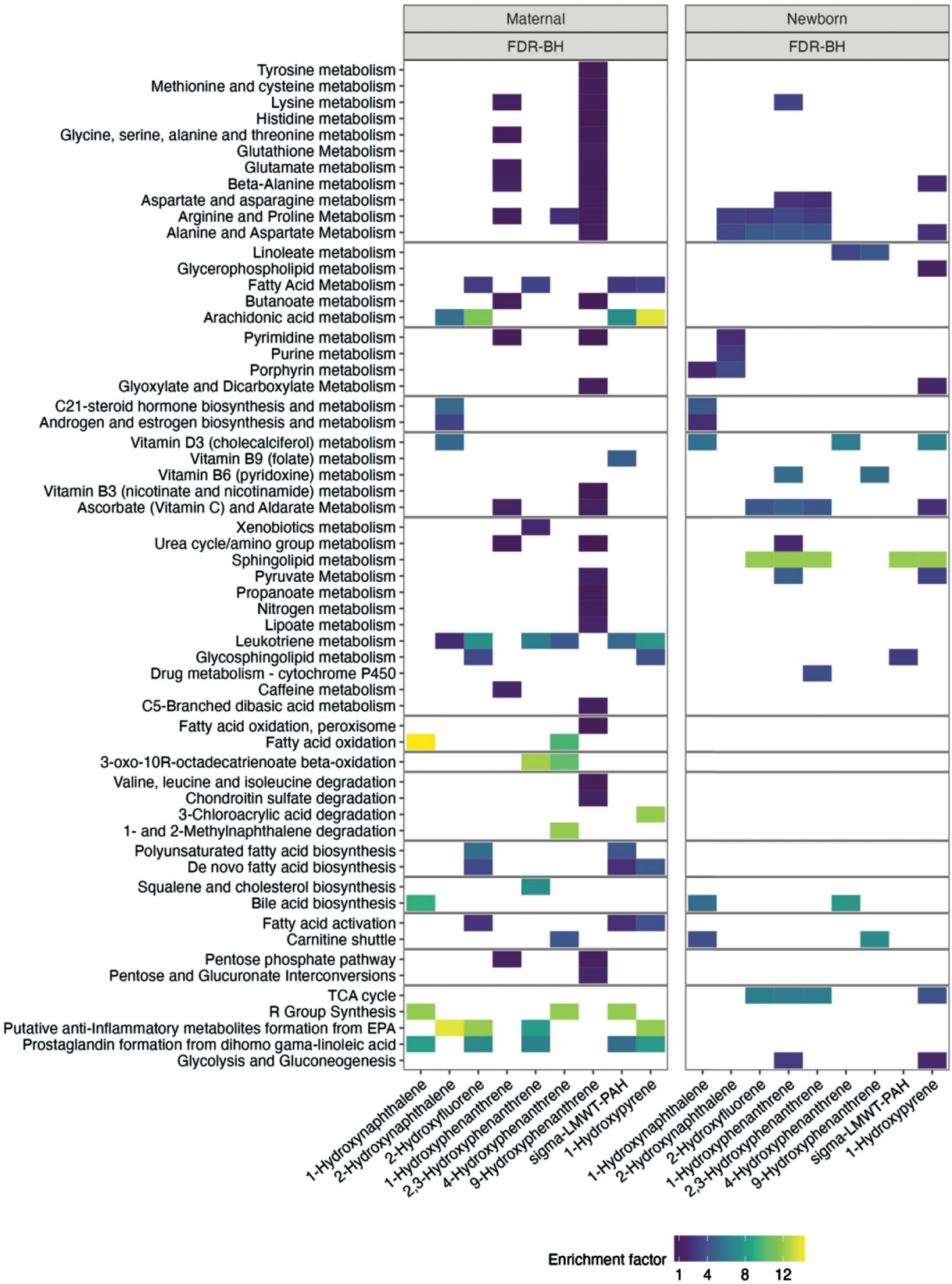

Fig. 2 Pathway analysis of PAH-associated metabolome from maternal and newborn serum. Above mentioned is a subset of pathways with significant associations. Analysis performed using mummichog algorithm considering Homo sapiens – MFN pathway library and limited to pathways with at least three entries

4 Discussion

In this study of a potentially vulnerable group, we assessed the association between maternal urinary PAH metabolites and maternal/newborn metabolome using an untargeted approach. Our results from the MWAS identified mostly positive associations between maternal urinary PAH metabolites and metabolomic features. Maternal PAH metabolites were found to be linked to various pathways, including metabolic processes involving vitamins, amino acids, lipids, carbohydrates, nucleotides, xenobiotics, and organic compounds. Whereas in newborns, the pathways associated with maternal PAH metabolite concentrations involve metabolism of vitamins, lipids, nucleotides, and carbohydrates. More maternal metabolic pathways were associated with PAH metabolites than newborn metabolic pathways, while 16 pathways were shared between mothers and newborns.

Overall, the urinary PAH metabolite concentrations observed in this study were relatively lower than compared to the National Health and Nutrition Examination Survey, except for 1-hydroxypyerene (Lu & Ni, 2023). Results from a pregnancy cohort that included 305 pregnant people indicated that higher concentrations of 1-hydroxypyerene metabolite could be associated with lower household income and education levels (Lin et al., 2023). This aligns with our study participants' profile with relatively lower household income and lacking college degrees. We considered 17,064 features that may represent exogenous or endogenous metabolites that could provide information on pathophysiologic changes at a cellular level as a result of PAH exposure (Elie et al., 2015; Lankadurai et al., 2013; Worley & Powers, 2013). Overall, we observed a higher volume (2% positive association vs. 0.6% negative) of positive associations between maternal PAH metabolites and newborn metabolome and similar positive/negative associations (2.1% positive and 1.8% negative) among pregnant women. The fraction of total metabolome features associated per PAH metabolite in pregnant women ranged from 0.94 to 14.06% and 1.31–7.01%. Our results suggest PAH metabolite related metabolome features significantly alter several pathways that covers metabolism, oxidation, degradation of amino acids, and biosynthesis. Modifications in amino acid metabolism/degradation pathways could impact on protein synthesis, lipogenesis, epigenetic modifications, redox homeostasis, and neurotransmission (Devignes et al., 2022). Enthoven et al. reported that the alterations in the amino acids, and urea cycle metabolism could be also due to the biological changes (maternal stress/unintentional intermittent fasting) among pregnant women (Enthoven et al., 2023). Alterations in fatty acid metabolism/oxidation, may result in an increased risk of type 2 diabetes and insulin resistance (Turner et al., 2014). Additionally, alterations in the biosynthesis/metabolism of corticosteroids may play a role in developing insulin resistance, fetal lung development, fetal sex differentiation, fetal growth, and development (McKay & Cidlowski, 2003; Sanderson, 2006; Wang, 2005).

Biological pathways related to PAH metabolites observed in this study are implicated in the etiology of adverse health effects previously associated with prenatal PAH exposure. To our knowledge, there were two studies conducted in the context of PAH exposures. These studies conducted in elderly/children, reported the plausible role of PAH exposure in the depletion of antioxidants, increased lipid peroxidation, dysfunction of mitochondrial lipid metabolism, breakdown of muscle proteins and upregulation of UDP-glucuronosyltransferases (Wang et al., 2015). In addition, Lu et al. reported metabolome changes associated with responses to oxidative homeostasis and delayed enzymatic de-induction (Lu et al., 2021). Although a fraction (17%) of the study participants smoked during pregnancy, PAHs could be from incomplete combustion of tobacco products (Vu et al., 2015). We observed several pathways (amino acid, lipid, and fatty acid metabolism) that overlapped between our results and studies that focused on maternal cotinine exposures during late pregnancy (Mueller et al., 2014; Tan et al., 2022).

Similarly, combustion of fossil fuel (ex: traffic or cooking) is one of the most common sources for PAH exposure, where PAHs could bind to particulate matter in the ambient air (Roy et al., 2019; Srogi, 2007). Liang et al., summarized several studies in context of air pollutant exposures (particulate matter), reported alterations in several biological pathways (amino acids, vitamins, and xenobiotics metabolism), that overlapped with our findings with PAH exposures (Liang et al., 2023).

In this study, we assessed the potential role of maternal PAH exposures in the maternal/newborn metabolome. Our results highlighted the potential role of maternal PAH exposures in adverse fetal development using an untargeted metabolomics approach. This approach allowed us to identify several small molecules that are associated with maternal PAH exposures and their potential role in human biological functions.

Due to the cross-sectional design of our study, the PAH metabolites measured in this study may not represent sustained exposure to PAHs. Due to the shorter half-life of the PAH metabolites, the maternal PAH metabolite exposure assessment during the delivery visit may introduce exposure misclassification bias. Although a majority of the study participants indicated living in the same residence throughout their pregnancy, this alone may not establish a longitudinal exposure profile of PAH exposures. Our results should be interpreted under the assumption that the study participants

lived in similar environmental conditions throughout their pregnancy. As annotating MS1 data may suffer from a higher false discovery rate, we limited our results by excluding metabolite annotations (Schrimpe-Rutledge et al., 2016). This limitation with metabolite annotations may increase the uncertainty of our findings from function analysis and to perform over representation analysis. To balance the uncertainty of our findings from the pathway analysis, we conducted a sensitivity testing by varying p-value threshold cutoffs to observe stable patterns. Our findings may be influenced by unmeasured confounders, small sample size, and having only one-time PAH exposure assessment. Moreover, the combination of relatively smaller sample size and the high dimensionality of metabolome features may introduce bias, potentially inflating the occurrence of false positives. Furthermore, the absence of a replication study hampers the validation of our findings. Nevertheless, a growing body of evidence highlights associations between prenatal exposure to air pollutants and adverse birth outcomes, with PAHs standing out as one of the primary toxicants linked to poor air quality (Nyadanu et al., 2022).

Our study highlights potential pathways that may be altered by PAH exposure. Further studies may be needed to quantify the potential mediating role of the metabolome in explaining the association between prenatal PAH exposures and pathophysiologic changes among newborns and children.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11306-023-02074-y.

Acknowledgements We acknowledge the staff assistance from Department of Obstetrics and Gynecology at University of Cincinnati in participant recruitment. We are thankful to our study participants for their time and efforts.

Author Contributions AC, JP, KEM, JMB, AMV, SMH, YKL, SSK, ZPP, EAD, and SH conceptualized the study. EDF collected maternal urine, for exposure assessment; and blood (maternal and cord) for metabolomics. DK processed blood samples for metabolomics. KEM, KDP, DPJ, and VT provided metabolomics expertise and performed untargeted metabolome assays. JP performed statistical analysis with guidance from AC, JMB, and KEM. JP drafted the manuscript. All authors reviewed, edited, and approved the final version of the manuscript.

Funding This research was funded by pilot projects from the National Institute of Environmental Health Sciences (NIEHS) and supported by the Center of Environmental Genetics (P30ES006096) at the University of Cincinnati. This project was also supported by grants from the Veteran Affairs [VA-I01BX005395 (SMH, YKL), VA-IK6BX006182 (SMH)], NIEHS [R01ES032675 (SMH, YKL), P30ES013508, R01ES028277 (AC), R01ES033054 (AC), R01ES032836 (JMB)], Department of Defense [DoD-W81XWH-22-1-0152 (SMH, YKL, AC)], and National Science Foundation [RII Track-2 FEC, Award #2217824 (SMH, YKL)].

Data Availability Raw data would be available upon request to the corresponding authors. The R code to perform the analyses are available via a GitHub repository: https://github.com/jagadeeshpuvvula/PAH_MWAS.

Declarations

Ethics approval All procedures performed in this study involve human subjects were in compliance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all the subjects included in this study.

Consent for publication All authors approve the manuscript for publication.

Competing interests The authors declare no competing interests.

References

Alshaarawy, O., Zhu, M., Ducatman, A., Conway, B., & Andrew, M. E. (2013). Polycyclic aromatic hydrocarbon biomarkers and serum markers of inflammation. A positive association that is more evident in men. *Environmental Research*, *126*, 98–104.

Amirdivani, S., Khorshidian, N., Dana, G., Mohammadi, M., Mortazavian, R., Quiterio, A. M., de Souza, S. L., Rocha, B., H. and, & Raices, R. (2019). Polycyclic aromatic hydrocarbons in milk and dairy products. *International Journal of Dairy Technology*, *72*, 120–131.

Barrett, E. S., Workman, T., Hazlehurst, M. F., Kauderer, S., Loftus, C., Kannan, K., Robinson, M., Smith, A. K., Smith, R., Zhao, Q., LeWinn, K. Z., Sathyanarayana, S., & Bush, N. R. (2022). Prenatal polycyclic aromatic hydrocarbon (PAH) exposure in relation to placental corticotropin releasing hormone (pCRH) in the CANDLE pregnancy cohort. *Frontiers in Endocrinology*, *13*, 1011689.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false Discovery rate: A practical and powerful Approach to multiple testing. *Journal of the Royal Statistical Society: Series B (Methodological)*, *57*, 289–300.

Brzeźnicki, S., Jakubowski, M., & Czerski, B. (1997). Elimination of 1-hydroxypyrene after human volunteer exposure to polycyclic aromatic hydrocarbons. *International Archives of Occupational and Environmental Health*, *70*, 257–260.

Centers for Disease Control and Prevention (CDC) (2019). Laboratory procedure manual - Urine Creatinine. Available at: https://wwwn.cdc.gov/nchs/data/nhanes/2017-2018/labmethods/ALB-CR-J-MET-Urine-Creatinine-508.pdf. Accessed on: April 06, 2023.

Devignes, C. S., Carmeliet, G., & Stegen, S. (2022). Amino acid metabolism in skeletal cells. *Bone Rep*, *17*, 101620.

Elie, M. R., Choi, J., Nkrumah-Elie, Y. M., Gonnerman, G. D., Stevens, J. F., & Tanguay, R. L. (2015). Metabolomic analysis to define and compare the effects of PAHs and oxygenated PAHs in developing zebrafish. *Environmental Research*, *140*, 502–510.

Enthoven, L. F., Shi, Y., Fay, E. E., Moreni, S., Mao, J., Honeyman, E. M., Smith, C. K., Whittington, D., Brockerhoff, S. E., Isoherranen, N., Totah, R. A., & Hebert, M. F. (2023). The Effects of Pregnancy on Amino Acid Levels and Nitrogen Disposition. *Metabolites* 13.

Gao, P., da Silva, E., Hou, L., Denslow, N. D., Xiang, P., & Ma, L. Q. (2018). Human exposure to polycyclic aromatic hydrocarbons:

Metabolomics perspective. *Environment International*, *119*, 466–477.

Harrison, R.J. (2021) Chemicals in LaDou, J. and Harrison, R.J. (Eds.), *CURRENT Diagnosis & Treatment: Occupational & Environmental Medicine, 6e*, McGraw Hill, New York, NY.

Henkler, F., Stolpmann, K., & Luch, A. (2012). Exposure to Polycyclic Aromatic hydrocarbons: Bulky DNA adducts and Cellular responses. In A. Luch, & Ed (Eds.), *Molecular, Clinical and Environmental Toxicology: Volume 3: Environmental toxicology* (pp. 107–131). Springer Basel.

Jedrychowski, W. A., Perera, F. P., Majewska, R., Mrozek-Budzyn, D., Mroz, E., Roen, E. L., Sowa, A., & Jacek, R. (2015). Depressed height gain of children associated with intrauterine exposure to polycyclic aromatic hydrocarbons (PAH) and heavy metals: The cohort prospective study. *Environmental Research*, *136*, 141–147.

Jedrychowski, W. A., Perera, F. P., Tang, D. L., Rauh, V., Majewska, R., Mroz, E., Flak, E., Stigter, L., Spengler, J., Camann, D., & Jacek, R. (2013). The relationship between prenatal exposure to airborne polycyclic aromatic hydrocarbons (PAHs) and PAH-DNA adducts in cord blood. *Journal of Exposure Science and Environmental Epidemiology*, *23*, 371–377.

Ji, S., Xin, H., & Su, E. J. (2019). Overexpression of the aryl hydrocarbon receptor nuclear translocator partially rescues fetoplacental angiogenesis in severe fetal growth restriction. *Clinical Science*, *133*, 1353–1365.

Johnson, W. E., Li, C., & Rabinovic, A. (2007). Adjusting batch effects in microarray expression data using empirical Bayes methods. *Biostatistics*, *8*, 118–127.

Kim, S. S., Vuong, A. M., Dietrich, K. N., & Chen, A. (2021). Proximity to traffic and exposure to polycyclic aromatic hydrocarbons in relation to Attention Deficit Hyperactivity Disorder and conduct disorder in US children. *International journal of hygiene and environmental health*, 232, p.113686.

Låg, M., Øvrevik, J., Refsnes, M., & Holme, J. A. (2020). Potential role of polycyclic aromatic hydrocarbons in air pollution-induced non-malignant Respiratory Diseases. *Respiratory Research*, *21*, 299.

Lankadurai, B. P., Nagato, E. G., & Simpson, M. J. (2013). Environmental metabolomics: An emerging approach to study organism responses to environmental stressors. *Environmental Reviews*, *21*, 180–205.

Li, S., Park, Y., Duraisingham, S., Strobel, F. H., Khan, N., Soltow, Q. A., Jones, D. P., & Pulendran, B. (2013). Predicting Network Activity from High Throughput Metabolomics. *PLOS Computational Biology 9*(7), e1003123.

Li, Z., Romanoff, L., Bartell, S., Pittman, E. N., Trinidad, D. A., McClean, M., Webster, T. F., & Sjödin, A. (2012). Excretion profiles and half-lives of ten urinary polycyclic aromatic hydrocarbon metabolites after Dietary exposure. *Chemical Research in Toxicology*, *25*, 1452–1461.

Liang, D., Li, Z., Vlaanderen, J., Tang, Z., Jones, D. P., Vermeulen, R., & Sarnat, J. A. (2023). A state-of-the-Science Review on High-Resolution Metabolomics Application in Air Pollution Health Research: Current progress, Analytical challenges, and recommendations for future direction. *Environmental Health Perspectives*, *131*, 056002.

Lin, Y., Craig, E., Liu, X., Ge, Y., Brunner, J., Wang, X., Yang, Z., Hopke, P. K., Miller, R. K., Barrett, E. S., & Thurston, S. W. (2023). Urinary 1-hydroxypyrene in pregnant women in a Northeastern US city: Socioeconomic disparity and contributions from air pollution sources. *Journal of Exposure Science & Environmental Epidemiology*, pp.1–9.

Loftus, C. T., Szpiro, A. A., Workman, T., Wallace, E. R., Hazlehurst, M. F., Day, D. B., Ni, Y., Carroll, K. N., Adgent, M. A., Moore, P. E., Barrett, E. S., Nguyen, R. H. N., Kannan, K., Robinson, M., Masterson, E. E., Tylavsky, F. A., Bush, N. R., LeWinn, K. Z., Sathyanarayana, S., & Karr, C. J. (2022). Maternal exposure to urinary polycyclic aromatic hydrocarbons (PAH) in pregnancy and childhood Asthma in a pooled multi-cohort study. *Environment International*, *170*, 107494.

Lu, L., & Ni, R. (2023). Association between polycyclic aromatic hydrocarbon exposure and hypertension among the US adults in the NHANES 2003–2016: A cross-sectional study. *Environmental Research*, 217, p.114907.

Lu, X., Lin, Y., Qiu, X., Liu, J., Zhu, T., Araujo, J. A., Zhang, J., & Zhu, Y. (2021). Metabolomic changes after Subacute exposure to Polycyclic Aromatic hydrocarbons: A natural experiment among Healthy Travelers from Los Angeles to Beijing. *Environmental Science & Technology*, *55*, 5097–5105.

Lubin, J. H., Colt, J. S., Camann, D., Davis, S., Cerhan, J. R., Severson, R. K., Bernstein, L., & Hartge, P. (2004). Epidemiologic evaluation of measurement data in the presence of detection limits. *Environmental Health Perspectives*, *112*, 1691–1696.

McKay, L., & Cidlowski, J. (2003). Physiologic and pharmacologic effects of corticosteroids. In D. W. Kufe, R. E. Pollock, R. R. Weichselbaum, B. RC, T. S. Gansler, J. F. Holland, & F. E (Eds.), *Holland-Frei Cancer Medicine*. BC Decker.

Miller, K. P., & Ramos, K. S. (2001). Impact of cellular metabolism on the biological effects of benzo [a] pyrene and related hydrocarbons. *Drug Metabolism Reviews*, *33*, 1–35.

Mueller, D. C., Piller, M., Niessner, R., Scherer, M., & Scherer, G. (2014). Untargeted metabolomic profiling in saliva of smokers and nonsmokers by a validated GC-TOF-MS method. *Journal of Proteome Research*, *13*, 1602–1613.

Nyadanu, S. D., Dunne, J., Tessema, G. A., Mullins, B., Kumi-Boateng, B., Lee Bell, M., Duko, B., & Pereira, G. (2022). Prenatal exposure to ambient air pollution and adverse birth outcomes: An umbrella review of 36 systematic reviews and meta-analyses. *Environmental Pollution*, *306*, 119465.

Onyemauwa, F., Rappaport, S. M., Sobus, J. R., Gajdosová, D., Wu, R., & Waidyanatha, S. (2009). Using liquid chromatography-tandem mass spectrometry to quantify monohydroxylated metabolites of polycyclic aromatic hydrocarbons in urine. *Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences*, *877*, 1117–1125.

Pang, Z., Chong, J., Zhou, G., de Lima Morais, D. A., Chang, L., Barrette, M., Gauthier, C., Jacques, P., Li, S., & Xia, J. (2021). MetaboAnalyst 5.0: Narrowing the gap between raw spectra and functional insights. *Nucleic Acids Research*, *49*, W388–W396.

Perera, F. P., Tang, D. L., Wang, S., Vishnevetsky, J., Zhang, B. Z., Diaz, D., Camann, D., & Rauh, V. (2012). Prenatal polycyclic aromatic hydrocarbon (PAH) exposure and child behavior at Age 6–7 years. *Environmental Health Perspectives*, *120*, 921–926.

R-Core-Team. (2022). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing.

Roy, R., Jan, R., Gunjal, G., Bhor, R., Pai, K., & Satsangi, P. G. (2019). Particulate matter bound polycyclic aromatic hydrocarbons: Toxicity and health risk assessment of exposed inhabitants. *Atmospheric Environment*, *210*, 47–57.

Sanderson, J. T. (2006). The steroid hormone biosynthesis pathway as a target for endocrine-disrupting chemicals. *Toxicological Sciences*, *94*, 3–21.

Sansen, S., Yano, J. K., Reynald, R. L., Schoch, G. A., Griffin, K. J., Stout, C. D., & Johnson, E. F. (2007). Adaptations for the oxidation of Polycyclic Aromatic hydrocarbons exhibited by the structure of human P450 1A2. *Journal of Biological Chemistry*, *282*, 14348–14355.

Schrimpe-Rutledge, A. C., Codreanu, S. G., Sherrod, S. D., & McLean, J. A. (2016). Untargeted Metabolomics Strategies—challenges and emerging directions. *Journal of the American Society for Mass Spectrometry*, *27*, 1897–1905.

Srogi, K. (2007). Monitoring of environmental exposure to polycyclic aromatic hydrocarbons: A review. *Environmental Chemistry Letters*, *5*, 169–195.

Stejskalova, L., Dvorak, Z., & Pavek, P. (2011). Endogenous and exogenous ligands of aryl hydrocarbon receptor: Current state of art. *Current Drug Metabolism*, *12*, 198–212.

Su, E. J., Xin, H., Yin, P., Dyson, M., Coon, J., Farrow, K. N., Mestan, K. K., & Ernst, L. M. (2015). Impaired Fetoplacental Angiogenesis in Growth-restricted fetuses with abnormal umbilical artery Doppler Velocimetry is mediated by Aryl Hydrocarbon Receptor Nuclear Translocator (ARNT). *Journal of Clinical Endocrinology & Metabolism*, *100*, E30–E40.

Suter, M. A., Aagaard, K. M., Coarfa, C., Robertson, M., Zhou, G., Jackson, B. P., Thompson, D., Putluri, V., Putluri, N., Hagan, J., Wang, L., Jiang, W., Lingappan, K., & Moorthy, B. (2019). Association between elevated placental polycyclic aromatic hydrocarbons (PAHs) and PAH-DNA adducts from Superfund sites in Harris County, and increased risk of preterm birth (PTB). *Biochemical and Biophysical Research Communications*, *516*, 344–349.

Tan, Y., Barr, D. B., Ryan, P. B., Fedirko, V., Sarnat, J. A., Gaskins, A. J., Chang, C. J., Tang, Z., Marsit, C. J., Corwin, E. J., Jones, D. P., Dunlop, A. L., & Liang, D. (2022). High-resolution metabolomics of exposure to Tobacco smoke during pregnancy and adverse birth outcomes in the Atlanta African American maternal-child cohort. *Environmental Pollution*, *292*, 118361.

Turner, N., Cooney, G. J., Kraegen, E. W., & Bruce, C. R. (2014). Fatty acid metabolism, energy expenditure and insulin resistance in muscle. *Journal of Endocrinology*, *220*, T61–T79.

United States Environmental Protection Agency (US-EPA) (1983). Polycyclic aromatic hydrocarbons: Evaluation of sources and effects, National Research Council, pp. ES 1–7. Available at: https://nepis.epa.gov/Exe/ZyPDF.cgi/9100V03I.PDF?Dockey=9100V03I.PDF. Accessed on January 30, 2023.

Uppal, K., Walker, D. I., & Jones, D. P. (2017). xMSannotator: An R Package for Network-based annotation of high-resolution Metabolomics Data. *Analytical Chemistry*, *89*, 1063–1067.

Vu, A. T., Taylor, K. M., Holman, M. R., Ding, Y. S., Hearn, B., & Watson, C. H. (2015). Polycyclic Aromatic Hydrocarbons in the Mainstream Smoke of Popular U.S. Cigarettes. *Chemical Research in Toxicology*, *28*, 1616–1626.

Walker, D. I., Lane, K. J., Liu, K., Uppal, K., Patton, A. P., Durant, J. L., Jones, D. P., Brugge, D., & Pennell, K. D. (2019). Metabolomic assessment of exposure to near-highway ultrafine particles. *Journal of Exposure Science & Environmental Epidemiology*, *29*, 469–483.

Wang, M. (2005). The role of glucocorticoid action in the pathophysiology of the metabolic syndrome. *Nutrition & Metabolism*, *2*, 3.

Wang, S., Chanock, S., Tang, D. L., Li, Z. G., Jedrychowski, W., & Perera, F. P. (2008). Assessment of interactions between PAH exposure and genetic polymorphisms on PAH-DNA adducts in African American, Dominican, and caucasian mothers and newborns. *Cancer Epidemiology Biomarkers & Prevention*, *17*, 405–413.

Wang, Z., Zheng, Y., Zhao, B., Zhang, Y., Liu, Z., Xu, J., Chen, Y., Yang, Z., Wang, F., Wang, H., He, J., Zhang, R., & Abliz, Z. (2015). Human metabolic responses to Chronic Environmental Polycyclic Aromatic Hydrocarbon exposure by a Metabolomic Approach. *Journal of Proteome Research*, *14*, 2583–2593.

Wickham, H., Averick, M., Bryan, J., Chang, W., McGowan, L. D., François, R., Grolemund, G., Hayes, A., Henry, L., Hester, J., Kuhn, M., Pedersen, T. L., Miller, E., Bache, S. M., Müller, K., Ooms, J., Robinson, D., Seidel, D. P., Spinu, V., Takahashi, K., Vaughan, D., Wilke, C., Woo, K., & H, Y. (2019). Welcome to the tidyverse. *The Journal of Open Source Software*, *4*, 1686.

Wieder, C., Bundy, J. G., Frainay, C., Poupin, N., Rodríguez-Mier, P., Vinson, F., Cooke, J., Lai, R. P. J., Jourdan, F., & Ebbels, T. M. D. (2022). Avoiding the Misuse of Pathway Analysis Tools in Environmental Metabolomics. *Environmental Science & Technology*, *56*, 14219–14222.

Wieder, C., Frainay, C., Poupin, N., Rodríguez-Mier, P., Vinson, F., Cooke, J., Lai, R. P. J., Bundy, J. G., Jourdan, F., & Ebbels, T. (2021). Pathway analysis in metabolomics: Recommendations for the use of over-representation analysis. *PLOS Computational Biology*, *17*, e1009105.

Worley, B., & Powers, R. (2013). Multivariate analysis in Metabolomics. *Curr Metabolomics*, *1*, 92–107.

Yim, S. H., Shah, Y., Tomita, S., Morris, H. D., Gavrilova, O., Lambert, G., Ward, J. M., & Gonzalez, F. J. (2006). Disruption of the Arnt gene in endothelial cells causes hepatic vascular defects and partial embryonic lethality in mice. *Hepatology*, *44*, 550–560.

Yu, T., Park, Y., Johnson, J. M., & Jones, D. P. (2009). apLCMS—adaptive processing of high-resolution LC/MS data. *Bioinformatics*, *25*, 1930–1936.

Yu, T., Park, Y., Li, S., & Jones, D. P. (2013). Hybrid feature detection and information Accumulation using high-resolution LC–MS Metabolomics Data. *Journal of Proteome Research*, *12*, 1419–1427.

Authors and Affiliations

Jagadeesh Puvvula[1] · Kathrine E. Manz[2] · Joseph M. Braun[3] · Kurt D. Pennell[2] · Emily A. DeFranco[4] · Shuk-Mei Ho[5] · Yuet-Kin Leung[5] · Shouxiong Huang[6] · Ann M. Vuong[7] · Stephani S. Kim[8] · Zana P. Percy[6] · Priyanka Bhashyam[9] · Raymund Lee[9] · Dean P. Jones[10] · Vilinh Tran[10] · Dasom V. Kim[11] · Aimin Chen[1]

✉ Jagadeesh Puvvula
Jagadeesh.Puvvula@pennmedicine.upenn.edu

✉ Aimin Chen
Aimin.Chen@pennmedicine.upenn.edu

1 Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

2 School of Engineering, Brown University, Providence, RI, USA

3 Department of Epidemiology, Brown University, Providence, RI, USA

4 Department of Obstetrics and Gynecology, College of Medicine, University of Cincinnati, Cincinnati, OH, USA

5 Department of Pharmacology and Toxicology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA

6 Department of Environmental & Public Health Sciences, College of Medicine, University of Cincinnati, Cincinnati, OH, USA

7 Department of Epidemiology and Biostatistics, School of Public Health, University of Nevada Las Vegas, Las Vegas, NV, USA

8 Health Research, Battelle Memorial Institute, Columbus, OH, USA

9 College of Arts & Sciences, University of Pennsylvania, Philadelphia, PA, USA

10 Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Emory University, Atlanta, GA, USA

11 Immunology Program, Memorial Sloan Kettering Cancer Center, New York, NY, USA