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Distribution and Predictors of Urinary Polycyclic Aromatic Hydrocarbon Metabolites in Two Pregnancy Cohort Studies

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Abstract

Pregnant women and their fetuses represent susceptible populations to environmental contaminants. Exposure to polycyclic aromatic hydrocarbons (PAHs) among pregnant women may contribute to adverse birth outcomes such as preterm birth. Multiple previous studies have assessed airborne sources of PAHs among pregnant women but few have measured urinary PAH metabolites which can capture total exposure through multiple routes. The aim of this study was to bridge this knowledge gap by assessing longitudinal urinary PAH metabolite concentrations over two time points in pregnancy cohorts in Boston (N=200) and Puerto Rico (N=50) to better understand exposure distributions throughout pregnancy and how they relate to demographic factors. Urine samples were analyzed for 1-NAP, 2-NAP, 2-FLU, 1-PHE, 2,3-PHE, 4-PHE, 9-PHE, and 1-PYR. Concentrations of 2-NAP, 1-PYR, and 4-PHE were higher in Puerto Rico, while all other metabolites were present in higher concentrations in Boston. In Puerto Rico, intraclass correlation coefficients (ICC) were weak to moderate, ranging from 0.06 to 0.42. PAH metabolite concentrations were significantly higher among younger, heavier (except 1-NAP and 9-PHE), and less educated individuals in Boston only. Consistent significant associations between PAH concentrations and measured covariates were not found in Puerto Rico. Our results suggest that potentially important differences in PAH exposure exist between these two populations.

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Additionally, our results indicate that multiple urinary measurements are required to accurately assess PAH exposure throughout pregnancy.

Graphical abstract

Keywords

Pregnancy; polycyclic aromatic hydrocarbons; exposure assessment

INTRODUCTION

Polycyclic aromatic hydrocarbons are compounds that are released as byproducts of incomplete combustion reactions. Outdoor air can be contaminated with PAHs from industrial combustion, wood fires, automobile exhaust, and asphalt (Agency for Toxic Substances and Disease Registry, 1995), while indoor air contamination can also occur through home heating and cooking emissions (Lewtas, 2007). Numerous PAHs have been classified as carcinogens by the International Agency for Research on Cancer (IARC (International Agency for Research on Cancer), 2010). Human exposure occurs via inhalation of indoor or outdoor air, ingestion of food, particularly grilled or smoked meats (Agency for Toxic Substances and Disease Registry, 1995), and exposure to tobacco smoke (Aquilina et al., 2010). Once in the body, PAH parent compounds undergo metabolic biotransformation resulting in hydroxylated metabolites which are then excreted in urine (Ramesh et al., 2004). Despite evidence of adverse health effects caused by PAHs, exposure is still widespread. Parent PAH compounds have previously been detected in studies worldwide assessing ambient (Jung et al., 2014) and personal (Tonne et al., 2004) air. Urinary metabolites (CDC, 2015; Urbancova et al., 2017) and DNA-adducts in blood and tissue (Perera et al., 2005a; Whyatt et al., 1998) have also been found. A positive association between PAH exposure and oxidative stress and indicators of cardiovascular disease morbidity and mortality has been demonstrated among occupationally exposed individuals (Brucker et al., 2014; Burstyn et al., 2005; Jeng et al., 2011; Wang et al., 2016). Although fewer in number, studies conducted among non-occupationally exposed populations have shown that urinary biomarkers of PAH exposure are positively associated with increased

serum CRP levels and total white blood cells counts (Alshaarawy et al., 2013), as well as childhood obesity (Scinicariello and Buser, 2014).

Pregnant women and the developing fetus are particularly sensitive to environmental exposures. Birth weight and birth size have been shown to be associated with PAH levels measured via dietary, personal and ambient air, and occupational exposures, as well as PAH-DNA adducts (Choi et al., 2006; Choi et al., 2012; Dejmek et al., 2000; Duarte-Salles et al., 2013; Jedrychowski et al., 2012; Langlois et al., 2014; Perera et al., 2005b; Tang et al., 2006). Developmental abnormalities including cephalization index (Polanska et al., 2014a), premature fusion of skull sutures (O'Brien et al., 2016), neural tube defects (Yi et al., 2015), and spina bifida (Langlois et al., 2012) have also been observed following *in utero* exposure to PAHs. A limited number of studies have shown pregnant mothers to be at increased risk of preterm birth when exposed to PAHs, but these and the previously mentioned pregnancy studies are limited by small sample size and number of cases (Choi et al., 2008; Guo et al., 2012; Singh et al., 2008), or by utilizing only outdoor air monitoring data for exposure assessment and ignoring dietary and indoor air exposures (Padula et al., 2014; Vassilev et al., 2001; Wilhelm et al., 2011).

The aim of this study was to evaluate and compare urinary PAH biomarker distributions among ongoing pregnancy cohorts in Boston and Puerto Rico, as well as with those reported in the US National Health and Nutrition Examination Survey (NHANES). We also set out to assess temporal variability of PAH concentrations measured in repeated urine samples collected from the same women at two time points during pregnancy, as well as demographic predictors of urinary PAH concentrations in these cohorts. Results of this study can be used to inform the most appropriate and efficient exposure assessment strategies in the design of future studies investigating the association between PAH exposure and adverse pregnancy outcomes.

MATERIALS AND METHODS

Study populations

Boston population—Beginning in 2006, women were recruited at their initial prenatal visit at Brigham and Women's Hospital (BWH) in Boston, MA, as part of the ongoing LIFECODES longitudinal cohort study. Inclusion criteria were: 1) recruitment prior to 15 weeks gestation; 2) maternal age >18; and 3) intention to deliver at BWH. As part of the study design, women provide urine samples for biomarker assessment at four visits during pregnancy (approximately 10, 18, 26, and 35 weeks gestation) which are stored for future biomarker assessment. From the women who delivered between 2006 and 2008 we selected 130 cases of preterm birth (delivery <37 weeks gestation) as well as 352 random controls, with the intention of examining maternal exposure to phthalates during pregnancy in relation to preterm birth (Ferguson et al., 2014). Pregnant mothers from this case-control population were median 33 years of age, primarily white (59%), did not use tobacco products during pregnancy (92.3%), and were of high socioeconomic status (80% with private rather than public health insurance providers) (Ferguson et al., 2014). In this exploratory analysis of PAH exposure, we selected 200 urine samples from the third study visit (median gestational age 26 weeks) for measurement. Half of the samples were from mothers who delivered

preterm and half were from term mothers. Throughout analyses within this population, we did not stratify based on case/control status as no differences were observed in this small subset (data not shown).

Puerto Rico population—The Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) study is a birth cohort study designed to investigate the relationship between environmental contaminant exposures and preterm birth on the island of Puerto Rico (Meeker et al., 2013). Recruitment began in 2010 and inclusion criteria were as follows: 1) maternal age 18–40 years; 2) residence within the study area (Northern karst region of Puerto Rico); 3) no use of contraceptives three months prior to pregnancy; 4) no use of *in vitro* fertilization for the present pregnancy; and 5) no known medical complications (Meeker et al., 2013). As part of the study protocol, participants provide urine samples at three visits in pregnancy. Mothers in this population are also largely non-smokers (97%), but are slightly younger than those from the Boston population (median age 27 years) and of lower socioeconomic status (44% household income <$20,000 per year) (Meeker et al., 2013). For the purposes of this study, we selected 50 participants who had urine samples stored from visits 1 and 3 for analysis of PAH metabolites (n=100 samples total).

NHANES population—In order to compare PAH concentrations from these study populations with those observed in the general US populations, we examined biomarker data from the National Health and Nutrition Examination Survey from 2011–2012 (Centers for Disease Control and Prevention, 2015). Using information from the demographic questionnaire, we restricted our analyses to female participants who were 18–40 years of age. For all analyses we included appropriate weights to account for the survey design, as described in detail on the NHANES website (Centers for Disease Control and Prevention, 2013b).

Urinary PAH metabolite measurement—For the Boston and Puerto Rico populations, urinary PAH metabolites were measured by isotope dilution-liquid chromatography with tandem mass spectrometry (LCMS) at NSF International (Ann Arbor, MI, USA). The parent PAH compounds, metabolites measured, and their abbreviations are listed in Table 1. The in-house LCMS method was developed and validated based on the approach previously described by Onyemauwa et al. (Onyemauwa et al., 2009). Samples underwent enzymatic deconjugation of glucuronidated species, online solid phase extraction, and analysis with a Thermo Scientific (Waltham, MA, USA) Vantage triple quadrupole mass spectrometer using multiple reaction monitoring in negative ionization mode. Urine sample online extraction was performed using a Thermo Scientific Cyclone P 0.5 × 50 mm turbulent flow extraction column followed by chromatographic separation using a Waters (Milford, MA, USA) Xbridge C18 5μm (3.0 × 150 mm) analytical column. The 2&3 hydroxyphenanthrene (2- & 3-OH-PHE) concentrations were quantitated together.

The precision of the method was determined by calculating the percent relative standard deviation (%RSD) of repeated measurements of the quality control (QC) materials throughout the validation. This value reflects both the intra-day and inter-day variability of the assay. The %RSD range for QC samples was 2.4–12%. The method accuracy was obtained through 6 replicate analyses of analytes spiked at three different concentrations in

human urine across validation runs on 3 separate days. The percent nominal concentration range across all analytes was 89–103 percent. Limits of detection (LOD) for hydroxylated PAHs are shown in Table 1. Values reported as below the LOD were replaced with the LOD divided by the square root of 2 (35.4 or 7.07). Values below the LOD that were reported numerically were kept at those values. In the Boston population one sample had 2-hydroxynapthalene (2-OH-NAP) and 1-hydroxynapthalene (1-OH-NAP) concentrations over the upper limit of detection and was removed from all analyses.

Methods utilized by the CDC for measurement of PAH metabolites in NHANES included isotope dilution gas chromatography with tandem mass spectrometry, and are described in detail elsewhere (Centers for Disease Control and Prevention, 2013a). As with our approach for PAH data from the other cohorts, levels below the LOD were replaced with the LOD divided by the square root of 2.

Statistical analysis

In the Boston and Puerto Rico populations we examined exposure distributions with selected percentiles in all samples measured. All PAH metabolites exhibited skewed distributions and were thus natural-log transformed to achieve normality in all statistical models. To explore changes in urinary concentrations over pregnancy within the Puerto Rico population we calculated intraclass correlation coefficients (ICC) between measurements from study visits 1 and 3 (Rosner, 2011). ICC represents the ratio of within to between individual variability, with an ICC of 1 indicating no variability between the two time points, and lower ICCs indicating greater variability. We also tested for differences by study visit using linear mixed models with ln-transformed PAH metabolite as the outcome and study visit as the predictor, with a random intercepts for each subject.

For the subsequent analyses comparing correlations and distributions across the three groups, we only included visit 3 PAH measurements from the Puerto Rico population to avoid issues arising from intra-individual correlation. First, we utilized Spearman correlation coefficients to examine correlations between urinary PAH metabolites in Boston and Puerto Rico separately. Second, we compared urinary PAH metabolite concentrations between study populations by creating boxplots for each metabolite and testing for differences using independent sample t-tests. Finally, to examine the relationship between demographic characteristics and urinary PAH metabolites, we calculated geometric means and 95% confidence intervals (CIs) for urinary concentrations within each category separately for the Boston and Puerto Rico populations. Differences in concentrations across categories were tested using linear models with ln-transformed PAH metabolites as the dependent variable. All analyses were performed using R version 3.2.3 and ICC were calculated using the ICC package (Wolak, 2015).

RESULTS

Limits of detection for all PAH metabolites were similar between NSF and CDC (Table 1). Distributions of urinary PAH metabolites in Boston measured at median 26 weeks gestation are presented in Table 2. Levels of 4-PHE were below the LOD in 37% of samples, while all other metabolites measured were detected in at least 85% of samples. Distributions of

urinary PAH metabolites in Puerto Rico measured at two time points during pregnancy are shown in Table 3. Like measurements in Boston, 37% of samples had levels of 4-PHE below the LOD and all other metabolites measured were detected in at least 85% of samples. PAH concentrations in Puerto Rico were generally lower than those in Boston, except for 2-NAP, 1-PYR, and 4-PHE which were higher in Puerto Rico.

Comparisons of urinary PAH metabolites in Boston, Puerto Rico, and NHANES are shown in Figure 1. All metabolites except for 1-PYR were statistically significantly different between Boston and Puerto Rico. Similarly, all metabolites were significantly different between Boston and NHANES except for 9-PHE which was not measured in NHANES. Fewer metabolites showed significant differences between Puerto Rico and NHANES, those being 1-NAP, 2-FLU, and 2,3-PHE. Additionally, levels of 1-NAP, 2-FLU, and 2,3-PHE were significantly higher in NHANES than both Boston and Puerto Rico.

Comparisons of geometric means of PAH metabolites by categorical covariates are given in Table 4. Levels of all PAH metabolites for those over the age of 25 (25–30, 30–35, ≥35) were significantly lower than for those under the age of 25 in Boston, while this was not the case for any metabolites in Puerto Rico. All metabolites tended to be higher among the youngest age group (<25) in both populations except for 1-NAP, which showed the highest levels among the oldest age group in Boston. Having a BMI ≥30 kg/m^2 was significantly associated with higher levels of all PAHs except 1-NAP and 9-PHE in Boston compared to the reference group (BMI < 25 kg/m^2), while this association was not observed in Puerto Rico. Higher education level (at least some college) was associated with lower levels of all PAHs in Boston relative to those with high school education or less, but this difference was not consistently significant. Similarly, those with education at the high school level or less had higher concentrations of 1-NAP, 2-NAP, 2-FLU, and 4-PHE in Puerto Rico, but these results also did not reach significance. Women in Boston who reported some smoking during pregnancy had significantly higher levels of 2-FLU than women who did not smoke during pregnancy. Levels of all other metabolites were higher among women who reported some smoking during pregnancy but were not significant. There were no women in the Puerto Rico sample who reported smoking during pregnancy.

Spearman correlation coefficients between PAH metabolites measured in both populations are given in Table 5. Correlations among metabolites were generally moderate to strong. Overall, correlation coefficients tended to be higher between metabolites in the Boston study compared to Puerto Rico, with the exception of 1-NAP. 1-NAP in both cohorts, as well as 2-NAP in Puerto Rico, tended to be less strongly correlated with the other metabolites.

There were no significant differences between PAH concentrations during visit 1 versus visit 3 in the Puerto Rico population (Figure 2). The ICC for 1-PHE was the strongest though only moderate (0.42), while the ICC for 1-NAP (0.06), 9-PHE (0.10), and 2-FLU (0.17) were quite weak. 2-NAP and 1-PYR both had borderline moderate ICC values (0.38).

DISCUSSION

This was one of the first studies to date to analyze urinary PAH metabolites among pregnant women in the US. Our results indicate that PAH metabolites were detectable in a high proportion of urine samples from two pregnancy cohorts in Boston and in Puerto Rico, which is consistent with results of a previous study showing detectable levels of various urinary PAH metabolites in pregnant women from NHANES (Woodruff et al., 2011). They were generally present at higher concentrations in the Boston women compared to Puerto Rico women except for 2-NAP, 4-PHE, and 1-PYR. Younger age and higher BMI were associated with some PAH concentrations in both cohorts. Using two repeated measures during pregnancy in the Puerto Rico cohort, we found weak to moderate ICC for PAH metabolites.

Few previous studies have been done assessing PAH metabolites in urine. One such study assessing personal air monitoring samples of 8 individuals while at home, at work, and commuting to and from work reported that levels of inhaled naphthalene were highest when the subject was at home, and also that total inhaled naphthalene was well correlated with levels of urinary 1-NAP, indicating that exposure to naphthalene likely occurs primarily through indoor inhalation (Li et al., 2010). In a similar study which also assessed both personal air samples and urinary PAH metabolites, urinary 2-NAP was associated with smoking and 1-PYR was associated with dietary exposures, while neither were well correlated with their inhaled parent compounds (Nethery et al., 2012). Another study looking at urinary PAH biomarkers found that increasing levels of serum cotinine were significantly associated with increasing urinary concentrations of 4-PHE (Polanska et al., 2014b). While we did not measure serum cotinine in our study, no women in the Puerto Rico population reported smoking during pregnancy, so the generally higher levels of both 2-NAP and 4-PHE found in Puerto Rico are unlikely due to primary smoking exposures.

Concentrations of 1-NAP and 2-NAP within each of the two populations in our study were only moderately correlated. In contrast to 2-NAP, 1-NAP is a urinary metabolite of exposure to both naphthalene and the insecticide carbaryl. It has previously been suggested that a ratio of 1-NAP:2-NAP which favors 1-NAP is indicative of exposure to carbaryl insecticides rather than naphthalene (Meeker et al., 2007). The low correlation between these two metabolites in our populations may suggest exposure to both parent compounds is occurring, and potentially more so in the Boston women. Mean exposure ratios in both of our populations favor 2-NAP, although less so in Boston, but further analysis at the individual level is necessary to determine specific sources of exposure.

Levels of 1-NAP were also only weakly to moderately correlated with any other PAH exposure biomarkers in either population. Similar results were found in a previous study in which all PAH metabolites except for 1-NAP measured in non-smoking, non-occupationally exposed individuals were strongly correlated within individuals exposed to a single dietary PAH source (barbequed chicken). In that study, after individuals with very high concentrations of 1-NAP relative to 2-NAP were removed from their analysis, levels of 1-NAP became strongly correlated with all other urinary PAH biomarkers (Li et al., 2012). Weak to moderate correlations between 1-NAP and other PAH biomarkers in our data may

indicate that individuals are differentially exposed to naphthalene and carbaryl. The Boston and Puerto Rico populations differed with respect to correlations between 2-NAP and all other metabolites, as well as correlations involving 2-FLU, 4-PHE, and 9-PHE. While 2-NAP was strongly correlated with other metabolites in Boston, it was only weakly to moderately correlated with any other metabolites in Puerto Rico. This may indicate a distinct source of exposure to 2-NAP that is present in Puerto Rico and not in Boston such as diet or other environmental sources that were not measured in the present study. Similarly, strong correlations were present between 2-FLU, 4-PHE, and 9-PHE in Boston but not in Puerto Rico, also potentially indicating that a common source of exposure for multiple other metabolites may be present in Boston that is not present in Puerto Rico. More detailed studies pairing personal exposure levels and dietary intake with exposure biomarkers would be needed to determine reasons for these observed differences.

We found weak to moderate ICC values in PROTECT that varied depending on the specific PAH metabolite. The range of ICC we reported for PAHs (0.06 – 0.42) are consistent with those reported for other non-persistent chemicals such as phthalates and phenols (Johns et al., 2015). However, a previous study among adult men reported an ICC between 0.55 and 0.61 for 1-NAP (Meeker et al., 2005), which is substantially higher than what we have reported here. Given the low to modest temporal reliability of a single measurement to represent exposure over months, multiple urine samples should be collected and analyzed during pregnancy to more accurately estimate exposure in epidemiology studies of gestational impacts on fetal and child health.

Younger groups generally had higher levels of all PAH metabolites in both populations, but the low number of individuals in the <25 age group in both populations make it difficult to ascertain true associations. Most PAH metabolites were significantly higher in subjects with a BMI of ≥30 kg/m^2 in Boston, which was not observed in Puerto Rico. The association of BMI with PAH concentrations in Boston may indicate that lifestyle factors are contributing more significantly to exposure there than in Puerto Rico. This was evident from associations with education level as well. In Boston, subjects with lower education levels had higher urinary PAH metabolite concentrations, but this was not observed in Puerto Rico. Small sample sizes within demographic categories in Puerto Rico in addition to underlying differences in education levels obtained between the populations should limit our interpretation of these differences.

One of the primary limitations of this study was that our sample sizes were small, particularly in the Puerto Rico cohort, so our power to detect statistically significant associations was limited. Additionally, it was outside the scope of the present study to measure PAH concentrations in environmental media and the diet that could contribute to PAH biomarker levels, making it difficult to ascertain the sources of PAH exposure in our cohorts. Differences in recruitment protocols between the populations could also be contributing to differences in PAH levels, however these differences are likely minor relative to geographic and demographic contributions. Despite these limitations, our study was novel in several ways. The PROTECT cohort was initiated to study the effects of environmental exposures on birth outcomes and has previously shown higher or comparable urinary concentrations of various environmental contaminants relative to those found in the US

population of reproductive aged women (Meeker et al., 2013). This was one of few studies conducted to-date assessing PAH exposure using urinary biomarkers among non-occupationally exposed populations. The use of biomarkers instead of air sampling methods to ascertain exposure levels is advantageous because it integrates all possible exposure routes and can account for accidental and unexpected sources of exposure. Also, use of biomarkers can account for issues resulting from inter-individual differences in genetics and metabolism compared to external measures of exposure (Lin et al., 2005). Finally, our study was unique in that we determined intraclass correlation coefficients of all PAH measures taken at different times during gestation in the Puerto Rico population.

CONCLUSIONS

In conclusion, we reported that PAH metabolites are detected in a high proportion of urine samples in two different pregnancy cohort studies, and that potentially important differences in patterns of the various metabolites were observed between the two studies. Younger age and higher BMI were associated with some PAH concentrations in both cohorts, findings that need to be further explained in future studies. Finally, we report weak to moderate ICC for PAH metabolites in samples collected approximately two months apart during pregnancy, suggesting multiple samples would be needed to accurately estimate gestational exposure to PAHs. These results provide evidence that the underlying cultural, geographic, and socioeconomic structures within populations are critical for understanding environmental exposures. Our findings should help the design of future epidemiology studies aiming to investigate associations between PAH exposure and adverse pregnancy outcomes and child development.

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HIGHLIGHTS

- PAH metabolites are detected in most urine samples in 2 distinct pregnancy cohorts
- High BMI and young age are associated with higher levels of some PAH metabolites
- Multiple measurements are necessary to accurately estimate gestational PAH exposure

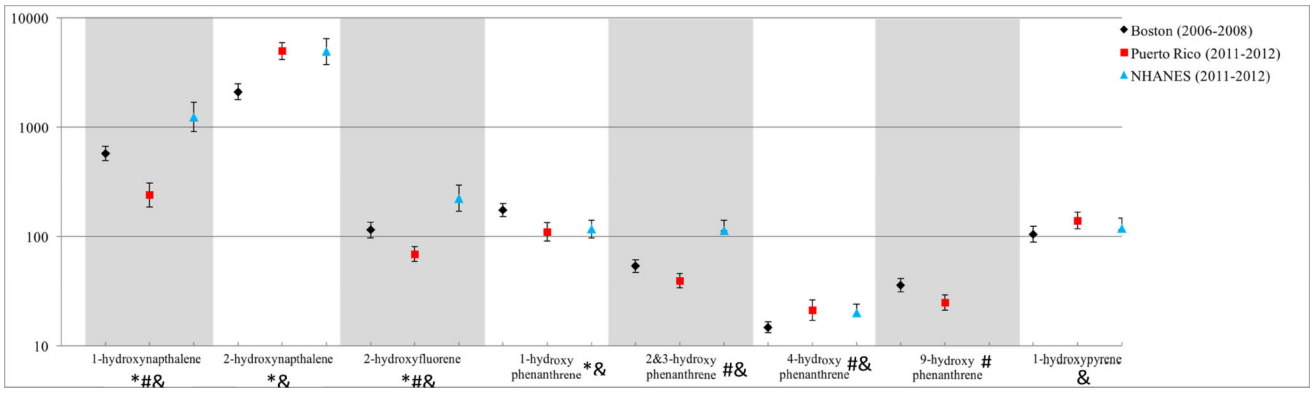

Figure 1.

Comparison of geometric mean (95% confidence interval) urinary PAH metabolite concentrations from pregnant women in Boston (n=199 samples from 199 women) and Puerto Rico (n=100 samples from 50 women), as well as levels in women of reproductive age (18–40) from NHANES (n=361).

Note: Sample sizes are as follows for each study population: Boston, n=200 samples from visit 3 of pregnancy for all metabolites except 1-NAP and 2-NAP, n=199; Puerto Rico, n=50 samples from visit 3 of pregnancy; NHANES, n=361 samples from women of reproductive age (18–40).

* indicates $p<0.05$ in Boston relative to Puerto Rico, # indicates $p<0.05$ in Puerto Rico relative to NHANES, & indicates $p<0.05$ in Boston relative to NHANES, determined via two sample t tests with unequal variance

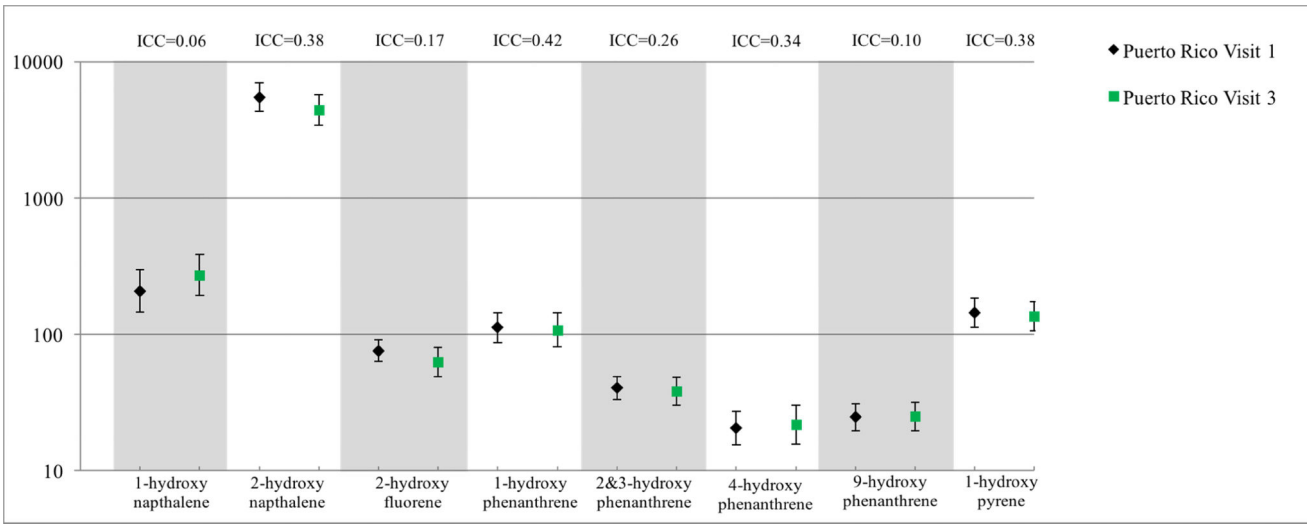

Figure 2.

Comparison of geometric mean (95% confidence interval) urinary PAH metabolite concentrations in visit 1 (median 18 weeks) vs. 3 (median 26 weeks) from pregnant women in Puerto Rico (n=50 samples for each visit) and intraclass correlation coefficients (ICC).

Table 1

Polycyclic aromatic hydrocarbons (PAH), urinary metabolites, abbreviations, and assay limits of detection at NSF International and CDC (ng/L).

PAH	Urinary metabolite	Abbreviation	NSF LOD	CDC LOD[1]
Napthalene	1-hydroxynapthalene	1-NAP	50.0	44.0
	2-hydroxynapthalene	2-NAP	50.0	42.0
Fluorene	2-hydroxyfluorene	2-FLU	10.0	10.0
Phenanthrene	1-hydroxyphenanthrene	1-PHE	10.0	10.0
	2-hydroxyphenanthrene	2&3-PHE	10.0[2]	10.0
	3-hydroxyphenanthrene			10.0
	4-hydroxyphenanthrene	4-PHE	10.0	10.0
	9-hydroxyphenanthrene	9-PHE	10.0	--
Pyrene	1-hydroxypyrene	1-PYR	10.0	10.0

[1] From NHANES 2011–2012.

[2] 2-OH-PHE and 3-OH-PHE quantitated together by NSF.

Abbreviations: NSF, NSF International, Ann Arbor, MI, USA; CDC, Centers for Disease Control and Prevention, Atlanta, GA, USA; LOD, limit of detection. Adapted from: http://www.cdc.gov/biomonitoring/Naphthalene_BiomonitoringSummary.html

Table 2

Distributions of polycyclic aromatic hydrocarbon (PAH) metabolites in urine samples collected from pregnant women in Boston at median 26 weeks gestation (n=200*).

		Percentile (ng/L)				
Metabolite	**% > LOD**	**25th**	**50th**	**75th**	**95th**	**Max.**
1-NAP	99%	293	562	1104	3358	16850
2-NAP	100%	913	1969	4957	12867	37780
2-FLU	98.5%	43.7	119	254	813	4493
1-PHE	100%	83.2	180	371	756	3227
2&3-PHE	96.5%	28.2	54.7	115	250	502
4-PHE	63%	< LOD	13.0	26.8	65.0	131
9-PHE	88%	16.3	37.1	66.6	179	652
1-PYR	96.5%	44.0	102	247	790	2859

Abbreviations: LOD, limit of detection; Max, maximum.

*Sample size is 199 for 1-NAP and 2 NAP and 200 for all other PAH metabolites.

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Table 3

Distributions of PAH metabolites in urine samples collected from pregnant women in Puerto Rico at two time points in pregnancy (n=100 samples, n=50 subjects).

		Percentile (ng/L)				
Metabolite	**N < LOD**	**25th**	**50th**	**75th**	**95th**	**Max.**
1-NAP	11	88.4	225	627	2111	9559
2-NAP	0	2679	5336	9226	19632	45192
2-FLU	1	39.9	67.6	112	216	2780
1-PHE	4	63.9	100	219	539	1234
2&3-PHE	4	26.6	39.5	64.3	118	521
4-PHE	37	7.1	18.9	43.8	149	520
9-PHE	12	13.5	24.2	36.4	120	646
1-PYR	0	133	245	579	1974	80.7

Abbreviations: Min, minimum; Max, maximum.

Note: no adjustment for repeated measures

Table 4

Geometric mean urinary polycyclic aromatic hydrocarbon (PAH) metabolites by categorical covariates in pregnant women from Boston and Puerto Rico.

Boston (n=200)		**N (%)**	**1-NAP**	**2-NAP**	**2-FLU**	**1-PHE**	**2&3-PHE**	**4-PHE**	**9-PHE**	**1-PYR**
Age category	<25	11 (5%)	670	6697	585	545	180	41.3	86.2	376
	25–30	38 (19%)	435*	2065*	108*	159*	50.8*	13.9*	30.7*	121*
	30–35	100 (50%)	559*	1940*	104*	161*	51.6*	14.4*	34.0*	99.0*
	≥35	51 (26%)	727*	1992*	103*	167*	45.6*	13.0*	35.6*	77.8*
BMI	<25 kg/m^2	97 (49%)	622	1804	90.5	146	43.8	12.9	34.9	81.8
	25–30 kg/m^2	56 (28%)	528	2181	119	168	53.6	14.8	31.4	99.6
	≥30 kg/m^2	47 (23%)	543	2757*	181*	260*	79.9*	19.2*	42.8	180*
Education	High school or less	27 (14%)	841	5363	407	375	135	31.2	69.1	287
	Some college	92 (46%)	482*	2154*	115*	169*	50.5*	14.4*	33.9*	106*
	College graduate	81 (40%)	618	1500*	75.6*	139*	41.7*	11.8*	30.0*	72.8*
Smoking	None in pregnancy	184 (92%)	556	2032	107	171	51.8	14.4	34.3	99.6
	Some in pregnancy	16 (8%)	845	3124	250*	208	74.9	19.5	52.3	172
Puerto Rico (n=50 from visit 3)										
Age category	<25	9 (18%)	554	4953	70.9	153	51.6	29.1	30.0	174
	25–30	16 (32%)	156*	4614	59.4	89.9	36.1	15.7	26.4	127
	30–35	15 (30%)	320	4489	70.1	110	36.9	25.5	22.4	143
	≥35	9 (18%)	254	3528	52.5	89.9	33.0	23.3	18.1	105
BMI	<25 kg/m^2	16 (32%)	166	4013	53.4	78.1	33.0	14.2	21.1	102
	25–30 kg/m^2	20 (40%)	388*	4679	64.2	118	41.1	27.7	27.6	157
	≥30 kg/m^2	11 (22%)	265	4541	67.9	113	36.7	24.8	19.9	149
Education	High school or less	3 (6%)	414	5377	85.4	121	47.2	35.1	25.2	168
	Some college	14 (28%)	339	4691	75.1	173	53.8	25.8	34.5	191
	College graduate	32 (64%)	233	4216	56.9	84.0	32.2	19.5	20.3	113

Abbreviations: BMI, body mass index.

*p<0.05 for difference from reference (first line for each covariate).

Note: All participants in Puerto Rico reported no smoking in pregnancy

Table 5

Spearman correlation coefficients for urinary PAH metabolites in pregnant women from Boston (upper triangle, white) and Puerto Rico (lower triangle, gray).

	1-NAP	2-NAP	2-FLU	1-PHE	2&3-PHE	4-PHE	9-PHE	1-PYR
1-NAP		0.31*	0.37*	0.34*	0.35*	0.40*	0.42*	0.32*
2-NAP	0.34*		0.75*	0.61*	0.70*	0.67*	0.65*	0.70*
2-FLU	0.48*	0.30*		0.87*	0.92*	0.81*	0.78*	0.84*
1-PHE	0.53*	0.24#	0.67*		0.92*	0.85*	0.76*	0.80*
2&3-PHE	0.49*	0.26#	0.78*	0.87*		0.91*	0.80*	0.86*
4-PHE	0.28*	0.13	0.46*	0.63*	0.59*		0.78*	0.78*
9-PHE	0.41*	0.29*	0.49*	0.71*	0.76*	0.32*		0.73*
1-PYR	0.45*	0.27#	0.67*	0.84*	0.86*	0.63*	0.69*	

*p<0.05,

#p<0.1

Note: Correlations from the Puerto Rico population are from samples taken at visit 3 only

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