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ORIGINAL PAPER

Predictors of Urinary Polycyclic Aromatic Hydrocarbon Concentrations: NHANES 2001–2006

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Abstract

Polycyclic aromatic hydrocarbons (PAHs) are hazardous air pollutants formed during incomplete combustion, absorbed through inhalation and ingestion, and metabolized to hydroxylated compounds that can be detected in urine. Biomonitoring data provide a direct way to link human exposure to environmental contaminants. However, these data do not reveal how various exposure routes or media contribute to the body burden of a specific chemical. We evaluated predictors of urinary PAH concentrations in 2001–2006 NHANES participants from reported information on demographic and housing characteristics, reported food intake, and modeled outdoor air pollutant exposures. NHANES participants were linked to their daily $PM_{2.5}$ exposure estimate and annual air toxics concentrations. Multivariate linear regression models were developed using the Deletion/Substitution/Addition algorithm to predict urinary PAHs. Exposure to air pollution was not associated with levels of urinary PAH metabolites. Current smoking status was the strongest predictor of PAH biomarker concentration and was able to explain 10–47% of the variability of PAH biomarker concentrations. In non-smokers, our prediction models were able to explain only 2–5% of the variability of PAH biomarker concentrations. Overall, our results indicated, with the exception of smoking status, there are not strong demographic, dietary, or environmental predictors of PAH exposure.

Keywords Biomarker · Polycyclic aromatic hydrocarbon · Air pollution

Introduction

Polycyclic aromatic hydrocarbons (PAHs) are hazardous air pollutants formed during incomplete combustion and are detected in food, air, and soil (ATSDR 1995). PAHs exist in the environment in both the gaseous and particulate phase. The United States Environmental Protection Agency (EPA) has included 16 PAHs on its list of hazardous air pollutants (US EPA 2016a). Many PAHs are semi-volatile organic compounds that partition in air between the vapor phase and particle phase as a result of adsorbing to atmospheric particulate matter (PM). PAH exposure often originates from the inhalation of cigarette smoke and polluted air from sources that include wildland fires, residential wood burning, waste incineration, and vehicle exhaust. PAHs can also be found in food through direct contamination from environmental and industrial sources, through preservation and processing procedures, and from grilling food (ATSDR 2009; Van Rooij et al. 1994).

PAHs readily enter the human body, and are transferred to blood through inhalation and ingestion and can be detected in urine as hydroxylated (OH) metabolites. Once inhaled or ingested, PAHs are metabolized primarily to hydroxy-PAH (OH-PAH) compounds; these compounds are biomarkers of exposure to the corresponding PAH parent compounds (Li et al. 2010). The metabolism and excretion process typically happens very quickly. For example, the half-life of pyrene is reported to be 3.9 h and 2.5–6.1 h for 9 other PAH biomarkers (Li et al. 2012). This means that urinary concentrations of these metabolites reflect exposure to PAH compounds mostly from the previous day. The International Agency for

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Research on Cancer has reported benzo[a]pyrene as a human carcinogen, benz[a]anthracene and dibenzo[a,h]anthracene as probable human carcinogens and benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, chrysene, and naphthalene as possible human carcinogens (IARC 2002, 2010, 2012). Exposure to PAHs also has been associated with lowered pulmonary and immune function and cardiopulmonary mortality (ATSDR 1995; Nadeau et al. 2010; Padula et al. 2015).

Traditional methods for assessing human exposure to PAHs have included biomonitoring and personal air sampling. Modeling has been used to characterize personal PAH exposure. Noth et al. (2011) combined meteorological data, emission sources in addition to other spatial variables with intensive home air pollution sampling to estimate and assign daily outdoor exposure (sum of 4-, 5- and 6-ring PAHs) to participants in the Fresno Asthmatic Children's Environmental Study. Researchers were able to explain 80% of the between-home variability and 18% of the within-home variability, with home heating fuel type and traffic characteristics as the main explanatory variables (Noth et al. 2011). Aquilina et al. (2010) utilized time-activity information and measured PAH concentrations in microenvironments to explain 25–45% of the variability in airborne pyrene concentrations. Wu et al. (2012) developed models to estimate personal concentrations of airborne particle-bound PAHs (PB-PAH) using location time activity, traffic activity, and questionnaire information. The researchers were able to explain 58% of the variability in personal daily exposure for PB-PAH, with the major predictors of exposure being time in vehicle, traffic count, and work-related exposures (Wu et al. 2012). Shin et al. (2013) revealed that modeled national data for PAH intake from outdoor and indoor emissions and food had the same range of cumulative distribution as urinary PAH metabolite concentrations among 2003–2004 National Health and Nutrition Examination Survey (NHANES) participants (Shin et al. 2013).

NHANES is an extensive cross-sectional health and nutritional study, in addition to biomonitoring, conducted by the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS). NHANES is a complex probabilistic survey that is representative of the non-institutionalized population of the United States. The survey assesses each participant's health, nutritional status, and for a subset of survey participants, the body burden of many different chemicals, including 4 PAHs—naphthalene, fluorene, phenanthrene, and pyrene (CDC (Centers for Disease Control and Prevention) 2012a, b, 2016). Biomonitoring provides a direct way to measure human exposure to environmental contaminants. However, these data do not reveal how various exposure routes or media contribute to the body burden of a specific chemical. The objective of this study was to evaluate predictors of urinary PAH concentrations in 2001–2006 NHANES participants from a variety of sources including demographic information, food intake, housing characteristics, and modeled outdoor air pollutant exposures.

Methods

Study Population

The study population consisted of adult individuals (age 20 years old and older) who participated in the NHANES surveys from 2001 to 2006. Interviews and questionnaires were used to obtain information on demographics, socioeconomic status, dietary intake, and household information. Next, participants completed a physical examination at a mobile examination center where their blood and urine were collected for laboratory analysis, including analysis for a range of exogenous and endogenous chemical substances. In a subsample of one-third of the total participants ($N=4579$), NHANES measured 8 urinary monohydroxy-PAH metabolites (ng/l; OH-PAH) which included 1-hydroxy-naphthalene, 2-hydroxy-naphthalene, 3-hydroxy-fluorene, 2-hydroxy-fluorene, 3-hydroxy-phenanthrene, 1-hydroxy-phenanthrene, 2-hydroxy-phenanthrene, and 1-hydroxypyrene (CDC (Centers for Disease Control and Prevention) 2012a, b, 2016). To quantify OH-PAHs, samples undergo enzymatic hydrolysis of the urine, followed by solid-phase extraction, and are analyzed using capillary gas chromatography combined with high-resolution mass spectrometry (Li et al. 2008). Concentrations that were below the limit of detection were replaced with the detection limit divided by the square root of two (CDC (Centers for Disease Control and Prevention) 2012a). Biomarker concentrations were adjusted for urine dilution by dividing each OH-PAH concentration by urinary-creatinine concentration (ng of PAH/g of creatinine). Next, OH-PAHs were summed by their parent compound to create four PAH biomarker variables—naphthalene (NAP), fluorene (FLU), phenanthrene (PHE), and pyrene (PYR).

From NHANES questionnaire data we obtained information on age, gender, race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black), education level (categories), and poverty status (categories), housing characteristics, and dietary intake. The NHANES questionnaire included a dietary recall of all foods eaten in the past 24 h. We considered their intake (yes/no) of 21 different foods or food groups (shellfish, poultry, meat, dairy, tea, coffee, fats and oils, cereal, wheat, rye, legumes, nuts, citrus, tomato, berry, other fruits, leafy vegetables, root vegetables, other vegetables, egg) previously associated with PAH contamination (ATSDR 2009; Duarte-Salles et al. 2010). NHANES participants were categorized as non-smokers, ever smokers, or current smokers, and

individuals who lived with smokers in the home. We also included the time of the exam session (morning, afternoon, evening) to account for differences in exposure to and metabolizing of PAHs throughout the day.

Exposure Data Sources and Exposure Assignment

For this analysis, a 2-day moving average for $PM_{2.5}$ was calculated to reflect an NHANES participant's exposure to $PM_{2.5}$ the day before and day of the NHANES examination. $PM_{2.5}$ exposure estimates were generated through a hierarchical–Bayesian (HB) modeling approach that was developed as a result of a collaboration between the EPA and the CDC Environmental Public Health Tracking Network. Daily 24-h mean $PM_{2.5}$ concentrations were created by combining $PM_{2.5}$ monitoring data from the EPA Federal Reference Method and numerical output from the Community Multi-Scale Air Quality numerical model in a Bayesian framework (McMillan et al. 2010). HB PM concentration estimates were provided in a 36×36 km grid across the United States for each day of years 2001–2006 (US EPA 2016b). To assign exposure estimates to each NHANES participant, the geographic centroid of each census tract in the United States was assigned to the HB PM estimate from the corresponding 36 km grid.

In addition, we used ambient annual total concentrations from 2002 and 2005 of PAH-particulate organic matter (PAHPOM02 and PAHPOM05), diesel exhaust (DPM02 and DPM05), and naphthalene (NAP02 and NAP05) obtained from the EPA National Air Toxic Assessment (NATA) (US EPA 2013). The following seven PAHs are classified as PAHPOM: benzo[a]pyrene, benz[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, dibenz[a,h]anthracene, and indeno[1,2,3-cd]pyrene (US EPA 2016c). The outdoor ambient total concentrations were estimated at the census-tract level using National Emissions Inventory data, which include major stationary, area, and mobile sources of hazardous air pollutants. Emission data are next input into the Assessment System for Population Exposure Nationwide model (ASPEN) and the Human Exposure Model (HEM). Both models incorporate atmospheric dispersion models and meteorological data as well as other factors affecting the concentrations of air toxic compounds, e.g., rates and height of emission releases, pollutant breakdown properties, and pollutant release parameters (stack height, emission rates, exit velocity (US EPA 2016d; Garcia et al. 2014; US EPA 2011). Because the NATA data were log-normally distributed, the natural log of each NATA exposure term (total ambient concentration) was used in the statistical analysis.

Exposure Assignment

Each NHANES participant who had measured levels of urinary metabolite levels was assigned exposure variables based on the census tract of residence and date of the NHANES exam. Census tract and exam date are restricted NHANES variables, and these data were accessed through the NCHS Research Data Center (RDC).

Statistical Analysis

We compared PAH biomarker geometric means (GM) across covariate categories from the NHANES dataset and compared differences in means using *t* tests. Because the PAHs had log-normal distributions of concentration, the natural log of each PAH metabolite was used in the statistical analysis. Next, we regressed each single exposure variable ($PM_{2.5}$, NATA total ambient concentrations, current smoking status) to each PAH biomarker (dependent variable) in a bivariate analysis (bivariate model). We used the public-use NHANES data and selected variables for multivariable linear regression models (MLRMs) to predict PAH biomarker concentrations (DSA model). In the statistical analysis, we included information on gender, age, education level, poverty status, and race/ethnicity categorized as Hispanic, non-Hispanic white and non-Hispanic black. Smoking information was used to categorize NHANES participants as nonsmokers, ever smokers, current smokers, and individuals that lived with a smoker in the home. Variables were selected and models were developed with the Deletion/Substitution/Addition (DSA) algorithm package in R Statistics. DSA is an aggressive model search algorithm that uses three steps: (1) a deletion step which deletes a covariate from the model, (2) a substitution step that switches one covariate with another, and (3) an addition step which adds a covariate to the model tested. DSA generates polynomial generalized linear models and includes a cross-validation step. Cross-validation is achieved by randomly splitting the datasets into 10 subsets, creating the MLRMs on 9 of the 10 sets, and comparing the predicted and measured PAH metabolites on the remaining set of the data (validation set) (Van Der Laan and Dudoit 2003; Sinisi and Van Der Laan 2004; Laan et al. 2006). For each PAH biomarker, the DSA was run 10 times with a different random seed number each time. The same model had to be selected for all 10 runs to be selected as the final model. If not, the DSA was run for an additional 10 runs (again with different random seeds used for each run) to find a final model that was consistently selected for 10 runs. The DSA algorithm was directed to include an intercept term, no interaction terms (for ease of interpretation), and allowed polynomial terms raised up to the power of 3.

Finally, we evaluated the predictive power of including each single exposure variable into the DSA models

(DSA-Exposure model). We forced each exposure variable one at a time into each DSA model because we were unable to use the DSA algorithm at the NCHS RDC. Because cigarette smoking was highly associated with all PAH biomarkers, we looked at current non-smokers separately. All descriptive statistics and regression models used SAS (version 9.1) survey procedures (PROC SURVEYMEANS and PROC SURVEYREG) to account for the complex survey sampling design. For all analyses, means and regression estimates were considered to be statistically significant if $p < 0.05$. Model fit was assessed by coefficient of determination (R^2). R v. 3.1.0 was used to run the DSA algorithm and ArcGIS 10.2 for spatial data processing and exposure assignment (SAS 2013; R Core Team 2013; ESRI 2014).

Results

In our sample of 4579 adult NHANES participants, 3549 were not current smokers; the number of measurements varied for each PAH biomarker (Table 1). PAH biomarkers were highly detected in NHANES participants with detection frequencies ranging from 95 to 100%. Naphthalene metabolite levels had the highest concentrations of all measured PAH biomarkers. Non-smokers had lower GMs compared to all adults of all measure metabolites (Naphthalene 4649 ng/g creatinine; fluorene 296 ng/g creatinine; phenanthrene 289 ng/g creatinine; pyrene 53 ng/g creatinine).

We estimated for all NHANES participants a 2-day arithmetic mean exposure to $PM_{2.5}$ of 10.9 g m^{-3} (Table 2). Geometric means for annual ambient air concentrations were highest for diesel particulate matter, followed by naphthalene and PAHPOM. Ambient concentrations of naphthalene and PAHPOM remained similar between the 2002 and 2005 assessment, while the concentration of diesel particulate matter decreased by 45% from 756.8 to 346.4 ng m^{-3}.

Table 3 presents the GM of each PAH biomarker in all NHANES participants included in our study across covariate categories selected by the DSA algorithm. These categories included time of day of NHANES exam, race/ethnicity, poverty level, smoking status and non-smokers who lived with a smoker, housing characteristics, and selected food intake variables. Not surprisingly, we observed significantly higher concentrations of all PAH biomarkers for individuals currently smoking cigarettes or individuals who lived with a smoker in the home. When compared to non-smokers, cigarette smokers had 127%, 142%, 60%, 98% higher concentrations for naphthalene, fluorene, phenanthrene, and pyrene metabolites, respectively. Participants living with a smoker in the home had 104%, 126%, 56%, 86% higher concentrations for naphthalene, fluorene, phenanthrene, and pyrene metabolites, respectively. Naphthalene and fluorene

Table 1 Descriptive statistics of PAH biomarkers in urine adjusted for creatinine in NHANES 2001–2006 participants

Parent PAH of metabolites (ng/g creatinine)	All adults		Non-smoking adults		Percent of metabolites > LOD[a] (range)
	N	GM (GSD)	N	GM (GSD)	
Naphthalene	4339	6571 (3.2)	3356	4649 (2.8)	100 (99–100)
Fluorene	4303	454 (2.9)	3324	296 (2.2)	99.7 (99–100)
Phenanthrene	4241	498 (2.4)	3271	286 (2.4)	99 (95–100)
Pyrene	4316	66 (2.8)	3329	53 (2.5)	99.1 (98–100)

GM geometric mean, *GSD* geometric standard deviation

[a]Percent > LOD is the average % of samples above the LOD over each individual metabolite of the parent PAH and the range across the survey years

Table 2 Descriptive statistics of exposure variables matched to all adult NHANES participants

Exposure (ng m^{-3})	Year	Mean[a] (95% CI)	GM (95% CI)	Percentile			Variable name
				5th	Median	95th	
$PM_{2.5}$ (g/m^3)	2001–2006	10.9 (10.1,11.7)	NA	3.70	9.29	23.1	PM2.5
PAH POM	2002	NA	10.39 (8.4, 12.8)	2.20	9.5	91.8	PAH POM 02
Diesel PM		NA	756.8 (675.6, 847.9)	262.6	839.4	2296.3	DPM 02
Naphthalene		NA	31.8 (25.6, 38.5)	3.8	37.6	247.6	NAP 02
PAH POM	2005	NA	10.15 (8.14, 12.6)	2.04	9.4	91.5	PAH POM 05
Diesel PM		NA	346.5 (273.1, 436.2)	37.75	454.8	2373.6	DPM 05
Naphthalene		NA	36.52 (31.6, 41.6)	NA	NA	NA	NAP 05

NA not available, *GM* geometric mean, *95% CI* 95% confidence interval of geometric mean

[a]Arithmetic mean

Table 3 Comparison of sample weighted geometric mean of biomarker concentrations across covariate categories selected by DSA algorithm in all adult NHANES participants

Parent compounds of metabolites		Naphthalene (ng/g creatinine)	Fluorene	Phenanthrene	Pyrene
	N	GM (95% CI)	GM (95% CI)	GM (95% CI)	GM (95% CI)
Time of exam					
Morning	2225	6465 (5959, 7014)	443 (409, 479)	**318** (301, 336)	69 (64, 74)
Afternoon	1671	**7069** (6515, 7670)	475 (433, 521)	338 (318, 359)	68 (63, 74)
Evening	683	6626 (5931, 7403)	477 (424, 536)	**361** (334, 391)	71 (64, 79)
Sex					
Male	2204	6135 (5664, 6646)	480 (442, 531)	318 (300, 337)	70 (64, 76)
Female	2375	**7257** (6689, 7872)	**441** (408, 476)	**345** (327, 363)	68 (63, 74)
Age group					
20 > 35 years	1347	5990 (5429, 6609)	441 (401, 484)	298 (278, 320)	72 (65, 80)
35 ≥ years	3232	**7010** (6523, 7534)	467 (433, 504)	**346** (331, 362)	68 (64, 72)
Race/ethnicity					
Hispanic	1069	**5992** (5408, 6639)	**358** (328, 390)	**263** (246, 281)	67 (63, 73)
Non-Hispanic White	2402	6732 (6211, 7297)	**479** (443, 518)	**353** (336, 370)	69 (64, 75)
Non-Hispanic Black	930	6904 (6186, 7297)	**499** (450, 553)	**302** (272, 335)	68 (60, 76)
Education level					
Non-high school graduate	1280	**8379** (7408, 9477)	**554** (510, 601)	**358** (336, 381)	**81** (73, 89)
High school graduate and above	3294	6382 (5926, 6873)	440 (411, 472)	326 (311, 341)	67 (62, 72)
Poverty status					
Above poverty	768	6468 (6056, 6907)	438 (410, 469)	326 (311, 342)	66 (62, 71)
In poverty	3549	**8955** (8024, 9994)	**647** (556, 753)	**377** (345, 411)	**94** (84, 106)
Smoking status					
Non-smoker	2379	4452 (4042, 4903)	290 (265, 317)	278 (260, 297)	52 (48, 57)
Current smoker	1030	**20**, **025** (18,475, 21,705)	**1732** (1865, 1608)	**518** (493, 543)	**151** (141, 162)
Home smoking					
No home smoking	3672	5279 (4663, 5975)	338 (303, 377)	294 (271, 319)	57 (52, 63)
Smoker in home	907	**16,907** (15,314, 18,665)	**1490** (1374, 1617)	**524** (493, 558)	**143** (133, 154)
Age of house					
20 years	427	5547 (4635, 6638)	424 (359, 502)	**292** (257, 331)	48 (40, 58)
30 years	477	6217 (4906, 7878)	450 (356, 570)	**313** (277, 354)	56 (45, 71)
40 years	652	6022 (4939, 7342)	429 (361, 509)	**327** (286, 375)	58 (49, 69)
50 years	345	5967 (4689, 7593)	**405** (338, 486)	**337** (293, 386)	59 (50, 70)
60 years	149	5497 (4078, 7410)	507 (357, 721)	348 (283, 426)	62 (48, 80)
70+ years	391	5571 (4647, 6678)	495 (421, 581)	400 (368, 435)	66 (57, 75)
Type of house					
Mobile home	371	**10**, **280** (7967, 13,262)	**653** (566, 755)	**367** (338, 398)	84 (72, 98)
Single-family detached	2809	**6301** (5790, 6858)	**433** (396, 474)	328 (310, 348)	66 (61, 72)
Single-family attached	381	7787 (6625, 9153)	489 (421, 567)	345 (299, 398)	68 (59, 79)
Apartment	939	6634 (5932, 7419)	478 (427, 535)	325 (299, 353)	75 (69, 81)
Other housing	44	5657 (4193, 7631)	504 (347, 731)	352 (271, 457)	75 (51, 109)
Home water source					
Water company	3937	6635 (6214, 7084)	453 (422, 487)	**327** (312, 342)	67 (63, 72)
Well water	550	7041 (5999, 8262)	498 (426, 581)	**362** (335, 391)	79 (69, 89)
Other sources	17	7282 (4257, 12,455)	479 (246, 935)	340 (254, 454)	86 (56, 132)
Dietary intake					
Meat					
Yes	2928	**6993** (6513, 7507)	**496** (460, 535)	**348** (330, 366)	73 (68, 78)

Table 3 (continued)

Parent compounds of metabolites		Naphthalene (ng/g creatinine)	Fluorene	Phenanthrene	Pyrene
	N	GM (95% CI)	GM (95% CI)	GM (95% CI)	GM (95% CI)
No	1651	6181 (5678, 6729)	400 (368, 435)	304 (286, 324)	62 (57, 68)
Tea					
Yes	1077	7181 (6533, 7893)	446 (408, 488)	346 (326, 367)	69 (64, 75)
No	3502	6535 (5765, 7409)	464 (413, 521)	327 (301, 355)	69 (63, 76)
Fat and oil					
Yes	2220	6404 (5976, 6963)	**429** (398, 463)	329 (312, 348)	63 (58, 68)
No	2359	7015 (6397, 7691)	493 (448, 542)	334 (312, 357)	76 (70, 83)
Tomato					
Yes	2030	6479 (6036, 6955)	**437** (408, 467)	338 (322, 355)	68 (63, 73)
No	2549	6871 (6275, 7524)	478 (440, 520)	326 (307, 346)	70 (65, 75)
Berry					
Yes	242	**8550** (7010, 10,428)	441 (369, 527)	353 (316, 393)	68 (59, 78)
No	4337	6585 (5322, 8147)	461 (386, 549)	330 (295, 369)	69 (60, 80)

Bold significant difference in mean biomarker concentration ($p < 0.05$). *95% CI* 95% confidence interval of geometric mean (GM)

metabolite concentrations were lower for individuals living in single-family detached homes, while participants living in mobile homes had significantly higher concentrations of naphthalene, phenanthrene, and fluorene metabolites. Phenanthrene metabolite concentrations increased with increasing age of the home and were higher in homes that used well water. Concentrations of naphthalene metabolites were significantly higher for participants sampled in the afternoon, while those for phenanthrene metabolites rose through the day. Gender differences were observed for metabolites of naphthalene, fluorene, and phenanthrene. Adult females had higher concentrations of naphthalene and phenanthrene and lower concentrations of fluorene compared to adult male participants. Older adults (35 ≥ years) had significantly higher concentrations of naphthalene and phenanthrene compared to younger adults (20 > 35 years). Participants who did not graduate high school or were below the poverty line (poverty to income ratio < 1) had significantly higher GM concentrations of all PAH biomarkers. When comparing food ingested the day before the NHANES exam, individuals who ate meat and berries had higher concentrations of naphthalene metabolites. Individuals who ate meat, fat and oils, and tomatoes had higher concentrations of fluorene metabolites, while only individuals who ate meat had higher concentrations of phenanthrene metabolites.

Final models that were selected by the DSA algorithm for each PAH biomarker stratified by current smoking status are presented in Table 4. For all adults, current smoking status and the presence of a smoker in the home (regardless of participant smoking status) variables were selected for every PAH biomarker model. The time of day for the NHANES exam was selected for fluorene and phenanthrene models in all adults and the phenanthrene model in non-smoking adults. Demographic factors such as gender, age, and race/ethnicity were selected among many of the DSA models. Of the 21 different foods considered, the ingestion of meat, tea, fat and oils, tomatoes, and berries was selected for each of the models. For pyrene, after 20 DSA runs, there was no consistent model selected for non-smokers.

Bivariate regressions indicated that PAHPOM, diesel particulate and naphthalene from 2002, PAHPOM from 2005, and $PM_{2.5}$ exposures were not associated with any PAH biomarker in all or non-smoking adults (Table S.1). Total ambient air concentrations of naphthalene from 2005 NATA showed a significant relationship with naphthalene ($p = 0.03$) and fluorene ($p = 0.02$) metabolite concentrations, while diesel particulates from 2005 showed a significant association with fluorene ($p = 0.02$) and phenanthrene ($p = 0.03$) metabolite concentrations. Current smoking status was able to explain 27, 40, 10, and 20% of the variability in the naphthalene, fluorene, phenanthrene, and pyrene metabolite concentrations, respectively (Table 4). The final models for each biomarker in all adults and non-smokers selected by DSA are presented in Table 4 with model fit (R^2) and regression coefficients in Supplemental Table S.2. In the multivariable DSA models selected, current smoking and home smoking were the strongest predictors of biomarker concentrations. NHANES participants who were above the poverty line had lower concentrations of fluorene in all adults and both fluorene and phenanthrene in non-smoking adults. In the full NHANES dataset, the multivariable DSA models explained 36, 51, 14, and 23% of the variability in the naphthalene,

Table 4 Regression models tested and model fit (R^2) in NHANES adults and non-smokers

Bivariate model[a]—($Y = {}_1$)	
All adults	
Model	R^2
NAP = current smoker	0.27
FLU = current smoker	0.47
PHE = current smoker	0.10
PYR = current smoker	0.20

DSA model[b] ($Y = {}_1 + {}_{2\ldots x}$)			
All adults		Non-smokers	
Model	R^2	Model	R^2
NAP = male + age + current smoke + house age^3 + home smoker + berry intake	0.36	NAP = male + white + age^2 + house age^3 + berry intake	0.05
FLU = age + age^2 + Hispanic + above poverty + house age + home smoker + current smoker + meat intake + oil intake + evening	0.51	FLU = home smoker	0.02
PHE = age + male + Hispanic + above poverty + HS grad + city water + current smoker + home smoker + tea intake + morning	0.14	PHE = age^2 + male + Hispanic + above poverty + well water + mobile home + home smoker + tea intake + tomato intake + evening	0.04
PYR = age^2 + male + city water + current smoker + home smoker + oil intake + meat intake	0.23	PYR = No model selected	

DSA-Exposure model[c]—(Y = Exposure ($_1$) + DSA-selected covariates ($_{2\ldots x}$))					
All adults			Non-smokers		
Model	Exposure (EXP)	R^2	Model	Exposure (EXP)	R^2
NAP = EXP + male + age + current smoke + house age^3 + home smoker + berry intake	PM2.5	0.36	NAP = EXP + male + white + age^2 + house age^3 + berry intake	PM2.5	0.05
	PAHPOM02	0.36		PAHPOM02	0.05
	DPM02	0.36		DPM02	0.05
	NAP02	0.36		NAP02	0.03
	PAPOM05	0.36		PAPOM05	0.06
	DPM05	0.36		DPM05	0.05
	NAP05	0.36		NAP05	0.05
FLU = age + age^2 + hispanic + above poverty + house age + home smoker + current smoker + meat intake + oil intake + evening	PM2.5	0.52	FLU = EXP + home smoker	PM2.5	0.02
	PAHPOM02	0.52		PAHPOM02	0.02
	DPM02	0.52		DPM02	0.02
	NAP02	0.52		NAP02	0.02
	PAPOM05	0.51		PAPOM05	0.02
	DPM05	0.52		DPM05	0.02
	NAP05	0.52		NAP05	0.02
PHE = EXP + age + male + hispanic + above poverty + HS grad + city water + current smoker + home smoker + tea intake + morning	PM2.5	0.14	PHE = EXP + age^2 + male + hispanic + above poverty + well water + mobile home + home smoker + tea intake + tomato intake + evening	PM2.5	0.06
	PAHPOM02	0.14		PAHPOM02	0.04
	DPM02	0.14		DPM02	0.04
	NAP02	0.14		NAP02	0.04
	PAPOM05	0.14		PAPOM05	0.04
	DPM05	0.14		DPM05	0.04
	NAP05	0.14		NAP05	0.06
PYR = PM2.5 + age^2 + male + city water + current smoker + home smoker + oil intake + meat intake	PM2.5	0.23	PYR = No Model Selected	PM2.5	–
	PAHPOM02	0.23		PAHPOM02	–
	DPM02	0.23		DPM02	–
	NAP02	0.23		NAP02	–
	PAPOM05	0.23		PAPOM05	–
	DPM05	0.23		DPM05	–
	NAP05	0.23		NAP05	–

[a]Only results for the current smoker bivariate analysis are presented here; all other bivariate analyses with the environmental exposure variables can be found in Supplemental Table S.1

[b]This model does not include any of the environmental exposure variables

[c]This model includes each environmental exposure variable plus all the DSA-selected variables

fluorene, phenanthrene, and pyrene metabolite concentrations, respectively, although most of the variability was explained by current smoking status. In the non-smokers NHANES dataset, the multivariable DSA models were able to explain only 5, 2, and 4% of the variability in the naphthalene, fluorene, phenanthrene, and pyrene metabolite concentrations, respectively.

Even when single exposures were added to each DSA model (Table 4; Supplemental Table S.3), current smoking was still the strongest predictor. DSA-Exposure Model results for all adults were able to explain 36, 52, 14, and 23% of the variability in the naphthalene, fluorene, phenanthrene, and pyrene metabolite concentrations, respectively, using all air pollutant exposures. Model prediction only increased slightly (1%) for fluorene metabolite concentrations. In non-smokers, these models were able to explain only 5, 2, and 4% of the variability in the naphthalene, fluorene, and phenanthrene biomarker concentrations, respectively, across all air pollutant exposures. In summary, the exposure variables explained as little as none of the variability and as much as 2% of the variability over that explained by the DSA model in all NHANES adults and in non-smokers.

Discussion

Our objectives were to assess associations between air pollution exposures and PAH biomarker concentrations and to evaluate if we could predict individual-level PAH biomarker concentrations from outdoor air pollutant exposures and from demographic, housing, and food intake information available from the NHANES survey. In our analyses, current smoking status was the strongest predictor of PAH biomarker concentration and was able to explain between 10% and 47% of the variability of PAH biomarker concentrations. The average concentration of these biomarkers was 2–6 times greater in smokers than in non-smokers, while other covariates differed by less than 20%. The DSA-selected models, which considered a wide range of participant characteristics and recent exposures, were able to explain only an additional 3–9% of the variability of PAH biomarker concentrations in all adults. In non-smoking adults, the best models explained only 2–5% of the variability in PAH metabolite concentrations, despite including home smokers in the fluorene and phenanthrene models. Using exposure variables with the DSA models provided only negligible improvement in model fit for fluorene in the full NHANES and phenanthrene in non-smoker NHANES. Overall, our results indicate, with the exception of smoking status, there are not strong demographic, lifestyle factors, diet, or environmental predictors of PAH exposure for the general population.

Our analytical approach was developed based on the work by Shin et al. (2013), who compared model-predicted PAH intake to PAH intake estimated from biomarker levels in NHANES participants (2003–2004) (Shin et al. 2013). They used log-normal probability plots to compare modeled and estimated PAH intakes and to infer a primary route of exposure for each PAH biomarker. Shin et al. (2013) suggested that the primary route of exposure for naphthalene, fluorene, and phenanthrene was inhalation of indoor air based on field studies that measured indoor concentrations, and for pyrene it was inhalation from both indoor and outdoor sources. They recommended that model predictions could be improved by including other potential exposure pathways such as cigarette smoking and food intake, which we were able to do in this analysis. For this reason, we sought to estimate individual-level outdoor air pollutant exposures for NHANES participants and explore if PAH urinary biomarkers were associated with any of these exposures, in the context of NHANES smoking and dietary data.

Lower molecular weight PAHs exist in the environment in the gas phase, while higher molecular weight PAHs are particle-bound (Naeher et al. 2007). Since many PAHs are semi-volatile compounds that adsorb onto atmospheric particulate matter (PM), PM concentrations are a proxy for the concentration of some PAHs in the atmosphere. However, ambient PM levels are not necessarily good predictors of actual PAH concentrations (Baek et al. 1991). Ambient PM can reflect the overall PAH concentration in air if both have similar combustion sources and there are no other sources of either, an assumption we made to complete this analysis. We did not detect any significant associations between $PM_{2.5}$ exposures and any PAH biomarker concentrations. However, Adetona et al. reported significant correlations between personal $PM_{2.5}$ exposure and creatinine-adjusted concentration of 2-hydroxy-fluorene and 1-hydroxy-phenanthrene (Adetona et al. 2012). The parent PAHs of the biomarkers that we evaluated have lower molecular weights and generally exist in the gas phase, with the exception of pyrene, which is perhaps why the PAHs we considered were not associated with $PM_{2.5}$ exposure.

Lu et al. (2014) conducted a controlled exposure study of diesel exhaust and concluded that urinary PAHs were not a promising biomarker of exposure (Leroyer et al. 2010). However, a controlled exposure experiment indicated that naphthalene and phenanthrene air concentrations could be used as surrogates for diesel exhaust exposure (Lu et al. 2014). We found that outdoor concentrations of diesel particulate matter were significantly associated with small decreases in urinary concentrations of fluorene and phenanthrene metabolites.

Exposure to modeled annual average naphthalene was significantly associated with an increase in concentrations of urinary metabolites of naphthalene and fluorene in all

adult NHANES participants in this study. Li et al. (2010) measured non-occupational exposure to PAHs through the measurement of personal air monitoring and urinary PAH biomarkers. Their study reported that inhaled naphthalene measured by personal monitors was correlated with total excreted urinary naphthalene metabolites (Li et al. 2010). Additionally, Leroyer et al. (2010) measured ambient PAH air concentrations and PAH metabolite biomarkers (1-hydroxypyrene and 3-hydroxybenzo[a]pyrene) and found that the measured air concentrations of pyrene, benzo[a]pyrene, or a sum of 16 PAHs was not correlated with PAH metabolite biomarker concentrations (Sobus et al. 2008).

Ingestion of PAHs through food has been suggested to be the dominant route of exposure for this class of compounds (Boström et al. 2002). Meat that is smoked, charred, or barbequed over wood or charcoal has a higher concentration of PAHs (ATSDR 1995; Li et al. 2008). Meat intake was chosen as a predictor by the DSA for fluorene and phenanthrene biomarkers. Tea was selected as a predictor of phenanthrene biomarkers in all adults and non-smoking adults and has been suggested as a source of dietary PAH exposure (ATSDR 2009). In the present study, berry and tomato intake were selected as predictors for urinary naphthalene in all and non-smoking adults and for urinary phenanthrene in non-smoking adults. Although they did not detect high concentrations, Duarte-Salles et al. reported that intake of fruit was a major contributor of total daily dietary intake of PAHs (Duarte-Salles et al. 2010). However, it should be noted that intake of these food sources increased the urinary PAH metabolites by only a small amount (generally less than 10%).

Across all the model factors that were tested in adult NHANES participants, current smoking was the strongest predictor of urinary metabolites of PAHs. In tobacco smoke, at least 539 PAHs and their alkyl derivatives have been identified, which makes smoking and second-hand smoke exposure important sources of PAH concentrations (St. Helen et al. 2012; IARC 2004). Past studies examining cigarette smoking have used 1-hydroxypyrene and 3-hydroxybenzo[a] pyrene as biomarkers of PAH exposure in smokers (Hecht 2002). St. Helen et al. (2012) investigated which PAH biomarkers were more selective for tobacco smoke for smokers with varying background outdoor air pollution concentrations (St. Helen et al. 2012). They found that 1-hydroxy-fluorene and 2-hydroxy-naphthalene were more selective than hydroxy-phenthranenes and 1-hydroxypyrene at indicating tobacco smoke (St. Helen et al. 2012); in this study we found that, compared to non-smokers, those who actively smoked had 6 and 4.5 times the concentrations of 1-hydroxy-fluorene and 2-hydroxy-naphthalene, and 1.9 and 2.9 times the concentrations of hydroxy-phenthranenes and 1-hydroxypyrene, respectively. Current smoking and the presence of a smoker in the home were the strongest predictors in the naphthalene and fluorene biomarker models.

Our results add to the literature examining the contribution of various exposure routes to the body burden of PAHs. In addition, we demonstrated a novel method that included assigning individual NHANES participants air pollution exposure estimates and used an aggressive model building tool, the DSA algorithm, with NHANES survey information. This approach could be used in future studies to examine routes of exposures and determine predictors of other biomarkers associated with environmental exposures that are measured in the NHANES.

A major limitation of our study is in the estimates of air pollutant exposures we used in our models. We did not have any direct daily personal PAH exposure data to use as predictors of urinary biomarker concentrations. We used an estimate of 2-day average $PM_{2.5}$ in the residential census tract of a participant as a proxy for ambient PAH exposure. Even though this was a spatially and temporally resolved exposure metric, it was not a good predictor of urinary PAH metabolite concentrations. Although NATA total annual average ambient exposure estimates included naphthalene and particulate PAHs, they were not strong predictors of urinary PAH biomarker concentrations. In contrast to the dietary data which represented intake 24 h before urinary sample collection, we could use only annual ambient PAH exposure estimates from the 2002 and 2005 NATA, which was for only 2 of the 6 years of NHANES survey data we used in our analysis. The concentrations for PAHPOM and naphthalene were similar in these 2 years; however, the DPM decreased by 45% from 2002 to 2005. Ambient PAH concentration varies dramatically across seasons and even from day to day within a season. PAHs have a short half-life in the body and are excreted relatively quickly as urinary metabolites, so annual estimates would not be expected to be good predictors of daily ambient exposures nor urinary PAH metabolite concentrations. In addition, we did not include any information on the occupation of the NHANES participants and thus have not accounted for any occupational PAH exposure.

Due to restrictions on the statistical programs and packages we were allowed to use at the NCHS RDC, we were unable to include the air pollution concentrations variables in the DSA model selection as candidate variables. The DSA was run separately with the public-use data, and air pollutant concentration variables were later incorporated into the DSA-selected models. It would have been informative to know if the exposure variables would have been selected as predictors of urinary PAH metabolite biomarkers by the same algorithm that selected the other predictor variables.

This study demonstrates how a rich dataset of urinary biomarker data and individual information on demographics, and food intake can be combined with estimates of air

pollution exposures to examine the contribution of multiple routes of exposure to body burden. In this case, the individual information on demographics, food intake, and air pollution exposure added very little to prediction models. Ambient air pollution exposures, both recent and annual average, did not explain much variability in the urinary PAH metabolite concentrations by themselves or when included in multivariate regression models, but the quality of the air pollution data was much less than that of the other data. In non-smokers we were not able to develop a multivariable regression model that explained more than 5% of the variability of urinary PAH metabolite concentrations. For the non-smokers, the presence of smokers in the home was the strongest predictor of both fluorene and phenanthrene metabolite concentrations. Current smoking status was the strongest predictor of urinary PAH biomarkers of exposure. Interestingly, although it has been speculated to be the main route of PAH exposure and the NHANES data quality was robust, ingestion of food in the 24 h prior to the exam was not a strong predictor of any urinary PAH biomarker. Further studies of routes of exposure of PAHs should be conducted to understand how exposure to PAHs in the environment contributes to the body burden of this class of toxic compounds.

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Compliance with Ethical Standards

Conflict of interest The authors declare no competing financial interests.

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